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Geomet Technologies, Inc.
Rockville, MD

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RESEARCH NEEDS

August 1981

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Project Group on Exposure and Metabolic Mechanisms

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U.S. Environmental Protection Agency • National Cancer Institute
National Heart, Lung, and Blood Institute • National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences • National Center for Health Statistics
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This report is the product of a workshop sponsored by the Task Force on Environmental Cancer and Heart and Lung Dsease. It contain 72 recommendations for basic and applied environmental research, which were developed through a consensus of scientific experts from Government, industry and academia. Research needs are identified in the following areas: accessing Federal data systems for epidemiological research; improving analytical techniques for monitoring and assessing human exposures; understanding mechanisms of activation and detoxification of environmental pollutants in animals and humans; examining the interactions of environmental pollutants with macromolecules, such as DNA; and understanding the repair and replicative processes, and gene expression as possible common toxicological events in cancer and heart and lung disease.

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SUMMARY OF THE WORKSHOP ON EXPOSURE TO ENVIRONMENTAL AGENTS, THEIR METABOLISM, AND MECHANISMS OF TOXICITY

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Please address your reply to:

To: Task Force on Environmental Cancer and Heart and Lung Disease

On behalf of the members of the Project Group on Exposure and Metabolic Mechanisms, it is my pleasure to submit our report describing research needs in environmental cancer and heart and lung disease. Due to the scope and complexity of these research needs, the Working Group decided to submit this report to Agency Directors for their review and consideration.

It should be mentioned that this report, which will accompany the Task Force Annual Report to Congress, resulted from a consensus of participating scientists from Government, industry, and academia who attended our Project Group's Workshop on Exposure, Metabolism, and Mechanisms of Toxicity, held on January 27-30 in Rockville, Maryland. A great deal of appreciation and recognition should be given to these panels of multidisciplinary scientists, who prepared position papers for discussion and reference purposes and worked extremely hard to produce the quality of research needs that address the important problems occurring in these environment-related diseases.

Research needs are identified in the following areas:

- Problems in gaining access to Federal data systems for epidemiological research.
- Monitoring of human exposure in the workplace or general environment through improved analytical techniques.
- New approaches that can be used to assess human exposure to pollutants in various environmental media.
- The importance of understanding detailed mechanisms of activation and detoxification of environmental pollutants and their potential effects on human health, particularly with respect to comparing such results in animals and humans.
- The modulation of toxicity that results from the interaction of environmental pollutants with critical cellular macromolecules and the consequences of these interactions to the host. This involves examining the interactions of environmental pollutants with such macromolecules as DNA, the repair and replicative processes, and gene expression as possible common toxicological events in cancer and heart and lung disease.

In addition to thanking all participants of the Workshop, Project Group members, and the members of the Task Force Working Group for their helpful suggestions, I would like to express my personal thanks to a number of hard-working individuals who made our Workshop a most successful effort:

- To Dr. Vilma Hunt, Chairman of the Task Force Working Group, who was very encouraging and supportive of our Project Group's efforts
- To the Chairmen and cochairmen who led the various subgroup sessions, most of whom are Project Group members:
    a. Drs. Tom Mason and Paul Leaverton (Exposure-Epidemiology)
    b. Drs. Herman Kraybill and Lance Wallace (Exposure-Quantification)
    c. Drs. Jim Gillette, Larry Hart, and Elizabeth Weisburger (Metabolism)
    d. Drs. Larry Loeb and James Trosko (Mechanisms of Toxicity)
    e. Ms. Peggy Young of GEOMET, who has worked so hard in helping me during the past 9 months of my association with the Task Force and has arranged all of the painful logistics in organizing the Workshop.

I hope that this report will be extremely useful in suggesting future research directions that should be pursued in addressing the problems of environmental cancer and heart and lung disease.

Respectfully submitted,

Morris I. Kelsey

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PREFACE

The Task Force on Environmental Cancer and Heart and Lung Disease, established by Congress under the Clean Air Act Amendments of 1977, is composed of representatives from the following Agencies:

U.S. Environmental Protection Agency (EPA)
National Cancer Institute (NCI)
National Heart, Lung, and Blood Institute (NHLBI)
National Institute for Occupational Safety and Health (NIOSH)
National Institute of Environmental Health Sciences (NIEHS)
National Center for Health Statistics (NCHS)
Centers for Disease Control (CDC)
Food and Drug Administration (FDA).

Congress directed the Task Force to recommend comprehensive programs and strategies for quantifying the relationships between two significant health factors: (1) environmental pollution and (2) cancer and heart and lung disease. The Task Force was directed to coordinate relevant research, stimulate cooperation among Federal Agencies, and report to Congress annually on its progress and difficulties in reaching these objectives.

The Task Force identified areas of special interest and created three interagency subcommittees, known as Project Groups, to address these special problems. This report documents the rationale and recommendations discussed by the Project Group on Exposure and Metabolic Mechanisms at meetings during the past year and developed in final form by invited expert scientists at a small workshop.

This Workshop on Exposure, Metabolism, and Mechanisms of Toxicity was held at the Sheraton Potomac Inn in Rockville, Maryland, January 27-30, 1981, to identify future research needs that are important in addressing the problems of environment-related cancer and heart and lung diseases. Prior to the Workshop, members of the Project Group selected a team of multidisciplinary scientists, who submitted position papers in their respective areas of expertise for reference and discussion. These scientists were then assigned to small subgroups, which drafted statements on rationale and research needs. After two Plenary Sessions, a consensus of those invited participants was reached regarding these research needs, and the document they generated was then reviewed before this report was submitted to the Working Group of the Task Force. With the exception of the first evening of keynote addresses, no formal presentations were made during this Workshop so that the participants could devote themselves to drafting the report to the Project Group.

The scope and nature of the research needs were quite varied and included (1) needs for gaining access to Federal data systems, (2) improved analytical methods for monitoring human exposure to environmental pollutants, (3) new approaches for assessing human exposure to multimedia agents, (4) a better understanding of detailed mechanisms of activation and detoxification of toxic pollutants and their impact on human health, and (5) more emphasis on the molecular events that follow genetic damage, and identification of those factors that modulate the toxicity resulting from these processes.

Therefore, the research needs in this report focus on approaches to the problems of environment-induced diseases from a multidisciplinary viewpoint and are contained in the major areas of exposure epidemiology, exposure quantification, metabolism, integration of toxicity, and mechanisms of toxicity/carcinogenicity. After review and approval by the Task Force Working Group and Plenary members, this report of research needs will accompany the Fourth Annual Report to Congress in August 1981.

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(The full text of keynote addresses appears in Appendix A.)

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INTRODUCTION

The realization that physical and chemical factors in the environment can profoundly affect human health has grown markedly during the past decades. Early efforts involved evaluating hazards of gross proportions, such as survival of individuals exposed to a toxic agent. Today's efforts have been extended to the most subtle effects measurable by modern technology after chronic exposure of individuals to toxic agents. Indeed, it has been evident for many years that the manifestation of cancers and certain kinds of heart and lung diseases occur only after prolonged exposure to the toxicants.

The ultimate objectives of environmental scientists and toxicologists are to identify natural substances in the environment that cause diseases in humans and other organisms and either eliminate them from the environment or decrease them to concentrations below which the incidence of disease would be negligible or acceptable. They also attempt to identify those manmade substances that cause diseases in humans and other organisms and the concentrations at which they cause significant incidence rates of the toxicities in humans and other species before they are introduced into the environment.

During the past several years, scientists have developed many approaches to achieve these objectives, including epidemiologic studies, long-term animal studies, and biochemical studies. Although much valuable information has been obtained with such studies, it has become increasingly evident that no single strategy is completely satisfactory in assessing the toxic potential of chemicals. Many of the approaches are based on assumptions that may not be universally valid. Unfortunately, the limitations of each of the approaches are not always obvious and not clearly understood.

In responding to the request from Congress, the current Task Force deliberately decided not to restrict its report to an enumeration of the many toxicologic studies currently being supported by the Government but instead to (1) look at current knowledge of the complex mechanisms by which chemicals cause various toxicities, (2) examine the factors that affect incidence rates in different individuals and biological species, (3) assess the strengths and weaknesses of the currently used strategies, and (4) determine possible new strategies that may ultimately be useful in describing the toxic potential of environmental chemicals.

Epidemiologic studies are primarily designed to discover relationships between the incidence of disease and the presence of potential toxicants already in the environment. However, the interpretation of such studies is fraught with difficulties, many of which are now obvious.

The fact that cancer and many heart and lung diseases are manifested only after prolonged exposure makes the identification of the toxic agent difficult. Indeed, most of the success in identification of human carcinogens and other toxicants by this approach has occurred only when the toxicant causes a unique type of cancer or other disease not usually occurring in humans.

The approach presumes that scientists have a reasonably complete catalog of the substances present in any given environment during the past two or three decades, which obviously is not true. Even if they had a complete catalog of environmental chemicals, it is still questionable that they would always be able to identify the toxicant because of its similarity to other chemicals.

The relationships between abundance of potential toxicants in the environment and present-day incidence rates of disease are also difficult to evaluate. Clearly, the incidence of delayed diseases, such as cancer and many heart and lung diseases, reflects the abundance of toxicants that have been present in the environment during the past two or three decades and not just the amount of the toxicant in the present environment. Thus, scientists need ways of estimating whether the amount of the toxicant has been increasing, decreasing, or remaining about the same during the past several decades. In cases of accidental release of pollutants into the environment, immediate monitoring of toxicants would be useful for prospective epidemiological studies. If the concentration of a pollutant is increasing, it is possible that current levels of pollutants may cause cancer in the future, even though current epidemiologic studies would suggest no relationship between the pollutant and disease.

Even when scientists are reasonably certain that a disease is caused by a given environmental chemical, the mechanisms by which the chemical causes the disease are frequently not understood. This is particularly true of cardiovascular and lung diseases. Thus, the possibility of intervening in the toxicity is largely unexplored.

Although the sequence of events in carcinogenesis is under intense investigation, most of the efforts are focused on early events, called "initiation," which alter the host's DNA. However, cells contain mechanisms that repair DNA and thereby tend to prevent initiation of carcinogenesis. In addition, however, cocarcinogens, tumor promoters, and nutritional, hormonal, and immunologic factors affect tumor growth and thus the manifestation of cancers.

Since humans and other animals outside of laboratories are remarkedly heterogeneous, some individuals or animal strains may be very sensitive to the toxic actions of chemicals, whereas others may be unusually resistant to them. Because of the diversities in the mechanisms of toxicity, however, a given individual may be highly sensitive to one toxicant and highly resistant to another. Because of these variations, however, elucidation of the reasons for these differences in susceptibility frequently proves useful in understanding the mechanism of the disease.

Therefore, the recommendations contained in this document are directed at efforts to link exposure information to studies of human epidemiology. Once establishing this linkage, basic mechanistic studies on the action of environmental pollutants should provide guidance on future strategies to minimize or eliminate the impact of these toxicants on human health.

CHAPTER 1. EXPOSURE-EPIDEMIOLOGY: NOVEL APPROACHES

I. OVERVIEW

Epidemiologic research on environmental cancer and heart and lung disease requires access to individually identifiable data. Federal data systems will need to be made accessible for such research. Since a number of studies that will be mandated require contacting persons, we believe it is desirable to utilize existing systems of records to minimize the invasion of privacy.

We believe that bona fide public health researchers have not in the past abused the privilege of studying individuals' records. In fact, we are aware of several major contributions to public health from such studies, and no instances of abuse. Thus, we do not feel that individual consent is required to protect the privacy of the person whose records are used solely for research.

In pursuing epidemiologic studies of environmental cancer and heart and lung disease, it must be recognized that most ambient environmental exposures are low dose. We believe that sensitive epidemiologic tools are required to quantify the association between exposure and response. We would encourage the use of morbidity studies in an attempt to quantify the relationship between exposure and response. These studies will require more specific data concerning the exposure(s) of the individuals under study than have been previously available.

A research area which may provide pertinent information concerning environmental exposure is damage to human reproduction. However, the epidemiology of human reproductive events is poorly described. We believe that damage to human reproductive function is not only a morbid event in itself but also a signal that damage leading to other forms of delayed, irreversible toxicity is perhaps taking place. While studies utilizing interview or other techniques aimed at discovering environmental or occupational hazards to reproduction are to be encouraged, basic epidemiologic studies of the phenomena of human reproduction are needed for valid scientific interpretation.

We commend the National Center for Health Statistics (NCHS), Health Care Financing Administration (HCFA), and Social Security Administration (SSA) for taking a number of appropriate steps to facilitate access to their data. The NCHS, through the development of the National Death Index, will greatly facilitate the ascertainment of the vital status of persons under study. The National Health and Nutrition Examination Survey, which is conducted by the NCHS, provides estimates of the prevalence of selected diseases and the establishment of baselines. The inclusion of physical examination, medical history, and dietary data greatly enhances the utility of this resource for epidemiologic studies. The NCHS has actively sought input from health professionals concerning ways to improve this survey and has made these data available.

The HCFA has made available a random sample of persons over 65 years of age for subsequent interview in large population-based case control studies. The HCFA is considering a regulation to permit additional access to their data. The SSA is also proposing a regulation that states that they will disclose information under appropriate circumstances for epidemiologic and similar research. We encourage both administrations to implement their proposed regulations as quickly as possible.

II. RECOMMENDATIONS

One of the major environmental causes of heart and lung disease and many cancers is cigarette smoking. We think that everyone should quit smoking. However, since people will continue to smoke, we recommend the following.

> RECOMMENDATION 1-1: More research on cigarette smoking is needed, particularly on the interaction between smoking and exposure to other potentially toxic agents.

We perceive numerous barriers to the efficient inception and completion of epidemiologic studies in Federal regulations on paperwork, privacy, and Freedom of Information. We do not believe it was the intent of Congress to so impede public health practice.

> RECOMMENDATION 1-2: A group such as the American Epidemiological Society or Institute of Medicine should be asked by Congress to report on and make recommendations concerning legal impediments to both Federal and non-Federal research.

There is an increasing need for studies to determine the relationships between environmental, occupational, and lifestyle factors and chronic degenerative disease. These studies are frequently very large, including thousands of subjects. With today's highly mobile population, investigators need a cost-effective mechanism for following persons and ascertaining their vital status.

> RECOMMENDATION 1-3: The NCHS should be provided sufficient resources, both monetary and personnel, to expedite the design, testing, and implementation of the National Death Index.

The geographic variations in cancer and heart and lung disease rates are impressive. This is one of the strongest arguments for environmental causation.

Our understanding of this variation is hampered by the fact that diseases are counted where they occur or where they produce mortality, not where they begin. Even if information on the residence histories of the study population is obtained, this information is not obtained for the population from which the subjects originate. Migrant studies (studies of people who move from one environment to another) would be possible in this country with relatively minor changes in current census activity.

> RECOMMENDATION 1-4: Additional information should be obtained by the Census Bureau that will more adequately describe migration patterns for population-based studies.

The work environment of many persons provides opportunity for exposure to substances that initiate or promote disease processes. We recognize that the prevention of morbidity among any work force depends on efficient occupational epidemiology. This requires maintaining records (e.g., exposure, medical, and personnel) and fostering an atmosphere of collaboration between persons responsible for maintenance of corporate records and epidemiologists.

The SSA maintains a wealth of information concerning work histories. However, data relevant to a decedent's work history now on file with the SSA cannot be accessed without prior authorization from the next-of-kin because of limitations placed by the Tax Reform Act of 1976. The SSA is able to reconstruct continuous work histories from quarterly earning reports for individuals. This information would be useful not only for confirmation of employment but also for such epidemiologic breakthroughs as a geographically based case-control study looking for excess employment in a specific industry.

There is another concern related to occupational studies. When conducting epidemiologic studies of working groups, investigators depend on historic company personnel records or labor union records to identify everyone who should be included in the study. However, these records often do not have information that is critical for the analysis of the study, i.e., race, sex, and date of birth.

> RECOMMENDATION 1-5: The SSA should not require next-of-kin authorization for the release of information from the quarterly earnings reports. We also recommend that the SSA provide such information as race, sex, and date of birth for persons under study when these data are not available from other sources.

We recognize the need for rapid registration and study of potentially exposed populations. We see the recruitment and maintenance of trained individuals such as epidemiologists and support staff as a problem since these individuals are in short supply.

> RECOMMENDATION 1-6: There is a significant manpower need for individuals trained in registration and study of potentially exposed populations.

CHAPTER 2. QUANTIFICATION OF EXPOSURE

I. OVERVIEW

Measurement of human exposure to environmental hazards, in the context of effects, is essential if we are to accomplish an effective exposure assessment. We recognize that although there are many efforts to measure exposure, much more needs to be done because data presently available for study are inadequate. The recommendations noted below assume that related needs for trained specialists in environmental health fields are recognized and plans are made for satisfying them.

The general recommendations that appear in this section relate to the following:

- The multidisciplinary approach
- Use of "experiments of nature," which involve not only humans but other species, such as animal pets, food-producing animals, controlled wildlife, and aquatic animals
- Protective factors that involve dietary substances, particularly macronutrient and micronutrient elements
- Sharing and integration of various data bases related to environmental factors (exposures) involved in cancer and heart and lung disease
- A holistic, integrative approach to develop a multisystems investigative model in which a substance is studied to reconstruct its entrance to the geochemical environment and its passage along the environmental pathways that reach and ultimately affect man and other animals in their environment
- Development of general criteria for assessment of toxicant exposure and associated health effects to facilitate methods development, quality assurance, and epidemiologic procedures.

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II. MULTIDISCIPLINARY APPROACHES IN ENVIRONMENTAL EXPOSURE

Much of the approach to research in the area of environmental cancer and heart and lung disease has been by a single discipline or by looking at a single aspect of the problem. Since these diseases are complex and multicausal, full understanding requires the application of knowledge from many disciplines.

> RECOMMENDATION 2-1: We urge a multidisciplinary team approach to research on cancer and diseases of the heart and lung because of the multicausal factors recognized in the etiology of disease. It is suggested that members of the team include biologists, chemists, epidemiologists, ecologists, nutritionists, pathologists, physicians, geneticists, physiologists, statisticians, toxicologists, and veterinarians. It is important to recognize that the population is constantly being exposed to a wide variety of pollutants in the air, water, and food, some of which occur naturally in the environment and contribute to "normal" background levels. Disease states and trends should be evaluated on the basis of the contribution of naturally occurring contaminants in all parts of the world.

III. RELEVANCE OF NONHUMAN LIVING SENSORS TO CANCER AND HEART AND LUNG DISEASE

Environmental factors as they relate to nonhuman health have often been evaluated in a controlled laboratory setting. This approach is encumbered by time and cost constraints, often with limited generalization to the natural experience in the general environment. Other than the effects on exposed humans, little attention has focused on other naturally exposed living sensors such as companion animal pets, food-producing animals, aquatic species, and controlled wildlife. It is recommended that nonhuman living sensors be given a priority consideration in investigating the effects of natural and manmade pollution, particularly as they apply to being predictors, accumulators, or part of the food chain.

RECOMMENDATION 2-2: There is growing evidence that domestic pets and certain aquatic species that share a specific chemical exposure with humans have a predictable disease response. Studies should be planned and conducted to determine the association between levels of exposure and disease states in animals and man. These studies require the calculation of disease frequencies, as well as chemical analyses of appropriate tissue.

RECOMMENDATION 2-3: Emphasis should be placed on determining the rates and extent of absorption of chemicals in animals by various routes of body entrance, how such variation affects response in target organs, and what factors control absorption.

RECOMMENDATION 2-4: Aquatic species, both fish and invertebrates, should be utilized as subjects in short- and long-term in vivo and in vitro laboratory exposure tests to key environmental pollutants in order to determine their accumulative capacities and biologic response profiles. These tests would address uptake, metabolism, physiological responses, and specialized responses such as carcinogenesis and teratogenesis. Results of these tests would identify aquatic species that are suitable models or predictors of effects and risks of pollutants in the general environment and in higher animal health. Results of these studies may provide invaluable data that link field effects in nature to specific agents.

IV. PROTECTIVE FACTORS THAT INVOLVE DIETARY SUBSTANCES, PARTICULARLY MACRONUTRIENT AND MICRONUTRIENT ELEMENTS

It is well known that some primarily nutritive elements can protect against some mainly toxic elements, e.g., iron/cadmium, calcium/lead, selenium/mercury. Turning to specific diseases, there is equivocal evidence to suggest that in human beings dietary deficiency of magnesium may increase the risk of some cancers (notably leukemia) and increase the risk of death from arteriosclerotic heart disease. And there is evidence to suggest that dietary intake of selenium at appropriate physiologic levels may reduce the incidence of cancer. With copper, experimental studies suggest that this important essential trace element may play a role in reducing the prevalence and/or severity of atherosclerosis and emphysema, particularly if deficiency is avoided during the period of development and early growth.

The evidence for all these effects, in terms of human disease, is equivocal, as stated above.

> RECOMMENDATION 2-5: The balance between positive and negative effects of the prevalence of inorganic cations and anions should be assessed, and the extent of adverse effects (cancer and heart and lung disease) evaluated in terms of prevailing concentrations in the geochemical environment. Geographic distribution, in terms of end results of these cations and anions, should be more precisely determined. Study populations should be selected based on studies designed to exploit the variability of geochemical environment exposures. There is also a need for experimental studies to define the mechanisms responsible for these observed effects.

V. INTEGRATION AND SHARING OF VARIOUS DATA BASES AND RESOURCES RELATING TO ENVIRONMENTAL FACTORS (EXPOSURE) INVOLVED IN CANCER AND HEART AND LUNG DISEASE

It is strongly urged that Federal Agency computer data bases be designed in a manner that will allow other interested Agencies ready access to the raw data to determine if other environmental factors influence the incidence of cancer and heart and lung disease. This will allow utilizing similar data from diverse sources in evaluating the influence of specific factors. For example, the data base developed by the Armed Forces Institute of Pathology (AFIP) is a resource to correlate pathological effects in man with recorded exposures reflected in levels of specific agents in human and animal tissue. These data need to be expanded by adding experimental and epidemiological studies conducted by other Agencies. After careful examination of the combined data, any suggested or presumptive evidence of cause and effect can be tested through appropriate studies.

In addition, the unique resource inherent in the Meat and Poultry Inspection program to detect evidence and follow trends in disease in livestock and poultry should be expanded to include detection of environmental contaminants and influence of these changes.

The above sharing of resources would allow testing of hypotheses and examination of data without having to duplicate work or observations already completed through the use of currently available technology or already-funded resources.

> RECOMMENDATION 2-6: Government Agencies should make available to qualified researchers their existing data bases that link exposure history with observed pathological conditions.
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> RECOMMENDATION 2-7: Data bases that correlate pathological effects in man with recorded exposures reflected in levels of specific agents in human and animal tissue should be extended by linkage with similar data bases.
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> RECOMMENDATION 2-8: We urge that functions of certain regulatory Agencies such as USDA be expanded to link monitoring of disease in farm animals with detection of environmental contaminants in order to investigate etiologic states relevant to human cancer.

VI. SYSTEMATIC HOLISTIC APPROACHES ON ENVIRONMENTAL CONTAMINANT EXPOSURE

In experimental work and probably epidemiological pursuits, dose-response investigations are oriented around a single toxicant that provides an exposure stress by one route of administration, and thus the assessment of an effect fails to take into account the possibility of multimedia exposure. This exclusion neglects consideration of environmental pathways through which this toxic agent(s) may traverse and the potential effect of an integrated stress on the organism--in other words, the "real world" situation.

RECOMMENDATION 2-9: Because man receives his exposures as an integrated stress by inhalation in the atmosphere, through absorption on the skin, or through ingestion in water and diet, such exposures should be qualified and quantified to arrive at a total exposure estimate. Animal experiments should be designed so that they provide for an assessment of the variant exposure situations which approximate or parallel those variant exposures in the human population.

CHAPTER 3. METHODS FOR MONITORING INDIVIDUAL HUMAN EXPOSURES TO ENVIRONMENTAL POLLUTANTS

I. OVERVIEW

Many authorities agree that the weakest link in our understanding of environmental health studies is our knowledge of human exposure. Until the last 2 or 3 years, there has been a very good reason for this ignorance: we simply could not measure hundreds of organic chemicals in our air, food, or water, nor could we measure their levels in breath, blood, or urine. Now, however, rapid progress is being made in trapping and measuring volatile organic compounds in all the environmental media and body fluids mentioned above. The major components of this advance have been:

- Development of sampling materials (such as Tenax GC) capable of collecting a broad spectrum of organic compounds quantitatively and reproducibly
- Development of sampling equipment (such as accurate pumps with miniature electronic circuits) allowing volunteers to collect 8-hour or 24-hour samples of the air at their breathing zones
- Development of analytical methods (such as gas chromatography/mass spectrometry) capable of detecting organic chemicals at the ambient (i.e., parts per billion) level in the media listed above.

Because of the rapid accomplishments, we believe it to be of high national priority that studies monitoring individual human exposure be conducted to put these advances to practical use. We have listed in our first recommendation four types of studies that are immediately needed.

At the same time, however, continued major efforts must be made in the area of improved sampling and analytical methodology. For example, hundreds of chemicals still cannot be analyzed in food. Our second recommendation deals with sampling, analytical, and microanalytical techniques: the basic area of research on which all future progress in exposure assessments rests.

The quality of our environmental exposure data has been rightly questioned, and our third and last recommendation suggests a strong national quality assurance program.

II. MONITORING HUMAN EXPOSURE

The great majority of governmental monitoring programs monitor surrogates of human exposure rather than exposure itself. For example, millions of dollars are spent yearly monitoring ambient outdoor air and water quality; yet many studies show that these data are not useful in estimating human exposure.

Now, however, newly available sampling and analytical methods make it possible to carry out extraordinarily fruitful monitoring programs, capable of multiplying manyfold our knowledge of the chemicals we are breathing, ingesting, and transforming in our bodies. We recognize four types of exposure monitoring studies that should be conducted by the appropriate Government Agencies.

Total Exposure

Because of fragmented agency responsibilities (workplace--OSHA; outside environment--EPA; inside environment--no Agency), monitoring studies are normally carried out in artificially limited ways. Even within Agencies, studies may be devoted exclusively to one medium (water, air, or food) even though major contributions to exposure may be through other media. Thus, each Agency should recognize its responsibility to consider in its monitoring programs the complete 24-hour exposures of the study population. This will involve direct measurements of a given chemical in the breathing-zone air, drinking water, and food and beverages of each individual in the study. Individuals should be selected to represent a wide range of activity patterns and related exposure.

Exposure/Dose Relationships

Concurrent measurement of exposure (through air, food, and water) and dose (as calculated from levels in breath, blood, urine, tissue, etc.) will identify the most important pathways of exposure for each compound and the most likely biological target for sampling. This will require both direct measurement in environmental and biological media and knowledge of metabolic pathways, or at least final metabolic products, in order to select the proper chemicals to monitor. Establishment of reliable correlation between exposure pathways and biological tissues or fluids would allow the selection of geographic areas of concern ("hot spots") through screening programs carried out on sample populations.

Baseline Studies

Present body burden data are heavily oriented toward metals, drugs, and pesticides. Considerable monitoring of organics in breath, blood, and urine should be done on normal-health individuals to obtain a baseline that can be compared with similar measurements in residents near manufacturing areas, toxic waste sites, or other geographic areas of concern. Similar considerations apply to gathering baseline environmental data in rural areas. These values will then be used to evaluate the findings of the first two types of monitoring studies described above.

Monitoring in Support of Epidemiology

The new sampling and analytical methods now make it possible to determine individual exposure for subjects of epidemiology studies. Nearly all previous environmental epidemiology studies have employed stationary monitors for measures of exposure. In most cases, outdoor measurements were made at a few fixed stations, even though the population under study was mobile and mostly indoors. (Recent studies indicate that outdoor fixed-station readings explain only 20 percent of the variance in human exposure.)

Now, however, the tools exist for measuring individual exposure in epidemiologic studies. These tools should be studied by epidemiologists, further developed to meet their needs, and used as integral parts of future epidemiologic studies.

For example, in assessing the health effects associated with exposure to chemical agents found in toxic waste sites, it is important not only that environmental monitoring be done at the immediate waste site but also that potential pathways for human exposure from leaching, volatilization, and windblown contaminated soil be identified and appropriate measurements taken to better identify the potential for exposure in segments of the population.

RECOMMENDATION 3-1: We believe that monitoring direct human exposure is more valuable than monitoring at fixed outdoor stations. Appropriate Government Agencies should reexamine their programs in the light of new techniques available and should redirect them when necessary to strengthen their exposure monitoring capabilities. At a minimum, the following four types of programs should be considered:

- Total exposure studies--consideration of all important pathways of exposure (i.e., air, food, water, skin absorption) and all important environments (work, home, commuting, etc.--24-hour exposure)
- Combined exposure/dose studies--direct measurement of exposure in air, food, and water concurrently with calculation of dose by measuring levels in blood, breath, urine, and hair
- Baseline monitoring--comprehensive surveys of "healthy" environments and people to establish baselines against which to compare results of monitoring "unhealthy" areas (toxic dumps, etc.)
- Monitoring in support of epidemiology--direct measurements of individual exposure to relate to the individual health effect being studied.

III. TECHNIQUES FOR MEASURING EXPOSURES

Sampling Techniques

The logical first step in determining exposure is collection of the sample. This seemingly simple requirement is in fact very complex. We breathe the air in our homes, work, and vehicles in varied patterns. Only by use of small monitors that can be with a person 24 hours a day can we hope to duplicate the actual exposure. The samplers must be light, quiet, and have a "memory" (either electronic or chemical). A few such personal monitors have been created; many more are needed.

As a second example, consider our foods. Grown in our backyards or shipped from overseas, they have such diverse histories that the experimenter is hard put to determine a way to sample food in a representative manner. The FDA Market Basket Surveys, which employ composite samples, are unable to estimate the range and variance of individual exposure.

The environmental samples should include breathing-zone air, food, water, and soil; the biological samples should include expired air, blood, urine, mother's milk, and saliva. The improvement of the sample collection techniques should be directed toward the preservation of the authenticity of the sample composition in the absence of artifacts; the provision of the sample in the most suitable form for the subsequent quantitative analysis; the acquisition of the sample with minimal invasiveness; and the final provision of noninvasive sampling techniques.

Analytical Techniques

Suitable analytical techniques must be available in order to measure chemicals in the environment to which man is exposed. This aspect of exposure assessment is critical if health effects are to be related to chemicals in the environment.

At present, techniques exist to measure many chemicals in water. Techniques have been partially developed for organic compounds in air (Tenax GC for volatile organics; polyurethane foam for pesticides, both followed by thermal desorption and gas chromatography/mass spectrometry analysis). Still needed are techniques for analyzing aerosols, asbestos, polyaromatic hydrocarbons, and other organics bound to particles. One obvious omission in current monitoring procedures is the extraction and/or analysis of nonvolatile organics, which may constitute a large component of human exposure. Farthest behind are techniques for analyzing food. Very recently, FDA has had some success with analyzing volatile organics in beverages, oils, and fish, but methods are lacking for hundreds of chemicals in different food groups.

In the area of biological tissues or fluids, analytical techniques for the determination of parent compounds and/or metabolites in blood, urine, and tissues of humans are required in order to estimate the dose of a chemical an individual has received. Because of metabolism and excretion rates, the time at which human samples are taken is important to the estimation of exposure levels. Recent work has succeeded in developing analytical techniques for breath, blood, and urine, but these techniques need to be improved, verified, and tested in the field.

Microanalytical Techniques

A crucial problem in estimating exposure is to gather a sufficient amount of a sample for later laboratory analysis. Yet an air sampler capable of collecting sufficient material to analyze carcinogens such as benzo(a)pyrene would be too bulky and noisy for a subject to carry about. Similarly, the need to obtain 20-40 cc of blood for each analysis is an extremely serious impediment to environmental research. The ability to analyze a few cubic meters of air or a few drops of blood for environmental chemicals of interest would allow for more widespread environmental studies.

> RECOMMENDATION 3-2: Despite recent encouraging progress, further advances in sampling and analytical techniques are urgently required to allow estimating human exposure and dose for hundreds of chemicals. These advances are needed along three broad fronts:

- Sampling Techniques--Of highest priority here is the development of personal air quality monitors for particulates, polyaromatic hydrocarbons, and fibrous aerosols (including asbestos). Monitors for formaldehyde, radon, and nitrogen dioxide capable of detecting 24-hour ambient exposures are desirable, but of less critical immediate need. A second priority is in the development of food sampling techniques capable of estimating individual (rather than aggregate average) exposures. A third priority is in developing sampling techniques for blood that are free from contamination.

- Analytical Techniques--Of highest priority is the development of techniques for analyzing chemicals in food, particularly volatile and nonvolatile organics. Second, techniques for analyzing asbestos, carbamate pesticides, and particulate organics in air are needed. Third, the further development and improvement of techniques for analyzing volatile organics in food, beverages, breath, blood, and urine are desirable.

- Microanalytical Techniques--Methods requiring very small samples should be developed and/or improved to minimize the invasiveness of the sample acquisition technologies. Then, focus the development on providing quantitative, sensitive, and reproducible analysis of both biological and environmental samples. Techniques that would provide analytical information suitable for subsequent computer-aided correlation should be developed.

IV. QUALITY ASSURANCE

Because of the extraordinary difficulty of collecting and analyzing environmental samples (as discussed above) and the large number of organizations collecting such data, high-quality data have been obtained only rarely owing to a lack of quality assurance.

Many laboratories produce environmental data whose quality is unknown due to differences in study design, sampling and storage practices, analytical methodology, and data handling. Voluntary quality assurance guidelines have proved ineffective in the past; EPA, for example, has instituted a mandatory quality assurance program.

RECOMMENDATION 3-3: A strong quality assurance program should be initiated for all Government-sponsored collection of environmental data. Results of quality assurance programs should be reported as an integral part of the exposure data. The program should include minimum requirements for blind, duplicate, and control samples, traceability to NBS standards, etc. Standards for many substances are not available and need to be developed by the National Bureau of Standards.

CHAPTER 4. METABOLISM

I. OVERVIEW

In considering possible ways of improving strategies to assess environmental cancer and heart and lung disease, it is important that scientists and Congress recognize the general nature of the diseases and the limitations of the various approaches currently used to assess them.

Other parts of this report have emphasized the importance of removing many of the legal restraints that impede epidemiologic studies. It is equally important, however, to realize that even under the best of conditions, epidemiologic studies by themselves will not provide all the information needed to discover the environmental etiology of cancer and chronic heart and lung disease. This is evident for several reasons: the incidences of such delayed diseases as cancer and many heart and lung diseases reflect the abundance of toxicants that have been present in the environment during the past two or three decades and not just the abundance of the toxicants in the present-day environment. Although it is obviously important to monitor known toxicants in current microenvironments in attempting to decrease toxicities, the rationale for monitoring substances of unknown or suspected toxicities in such microenvironments is less obvious. Clearly, the monitoring of such substances present in the environment in rather constant amounts during the past few decades should be useful in elucidating possible relationships between the occurrence of the substances and the incidence of disease. But the monitoring of newly introduced substances or of substances whose concentrations have changed markedly during the past few years would be of questionable value unless such studies are integrated

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with plans to follow exposed cohorts in long-term prospective epidemiologic studies. Such studies, however, are inherently expensive.

To obtain maximal information from epidemiologic studies, it is important to realize that most of our knowledge of environmental diseases has been initiated by the observations of astute victims and astute individual physicians and not by broadly based epidemiologic studies. Indeed, most of the success in identification of human carcinogens and other toxicants by the epidemiologic approach has occurred only when the toxicant causes a type of cancer or other disease occurring rarely in humans. It is, therefore, important that teams of specialists be available to evaluate the suspicions of victims and physicians. It is also important to realize that humans are remarkably heterogeneous in their susceptibility to environmental diseases. Thus, some individuals may be very sensitive to the toxic actions of chemicals, whereas others may be very resistant to them. Because of the diversities in the mechanisms of toxicity, however, a given individual may be highly sensitive to one toxicant and highly resistant to another. It is likely, therefore, that those individuals who present with an environmental disease are unusually sensitive to the toxicant.

II. RECOMMENDATIONS

RECOMMENDATION 4-1: Efforts should be made to determine whether the manifestation of the disease may be associated with unusual physiological or biochemical differences in the individual. Whenever possible, such investigations should include studies on the pharmacodynamics and pharmacokinetics of the suspected toxicant, hypersensitivity reactions, and abnormal cellular biology. Geneticists should be included in the team of investigators to determine whether the abnormalities are genetic or environmental in origin.

The mere fact that we are recommending that epidemiologic studies be continued, especially with substances that are newly introduced into the environment, represents the realization by scientists that other approaches will not always be completely effective in preventing the introduction of toxic chemicals into the environment. Because of the marked heterogeneity of human sensitivity to toxicants, it is unrealistic to expect that any animal model will exactly duplicate human susceptibility to toxicity or human variability in response to environmental chemicals. All animal models will have limited applicability in toxicologic evaluation. Indeed, the most that can be hoped for is that the data obtained from an animal model may be applicable to the majority of humans, not all of them. Nevertheless, animal models, when properly studied, can provide information about the potential of substances to cause toxic effects under certain defined conditions.

> RECOMMENDATION 4-2: The advantages and limitations of animal models must be generally appreciated. Animal models are useful in determining whether toxicities are mediated by the parent substance, by one of its stable metabolites, or by a short-lived metabolite. Moreover, some animal models are uniquely sensitive to the toxic actions of environmental chemicals and thus toxic actions that affect relatively small numbers of persons may be predicted. Research should be supported to determine ways in which genetic traits and environmental factors can modify the toxicity or environmental chemicals in animals. Such studies should include searches for the type of genetic traits and environmental conditions that could be important in evaluating possible human susceptibility to environmental toxicants. Indeed, studies on the mechanisms of toxic effects known to occur in humans are frequently hampered by the lack of animal models that exactly mimic humans.

It is usually not even valid to extrapolate the incidence rate or a toxicity observed in a single homogeneous strain of a given animal species to another strain of the same animal species, much less to extrapolate such data to other animal species. Although strain differences in the incidence rate may be due to any combination of a number of causes, they are frequently due to differences in the metabolism of the toxicant. On the other hand, it is seldom possible to predict toxicity of a substance solely by studying the metabolism of the substance in the animal strain.

> RECOMMENDATION 4-3: The pattern and kinetics of metabolism in animals may change with the dose of the substance, with the season of the year, with the presence of other substances in the environment, or with multiple dosing; therefore, research on the toxicity of environmental chemicals should be accompanied by studies on the disposition of the chemical and its metabolites in the same animal cohort over a range of doses including the highest and lowest doses of the compounds used in the toxicologic test at several times during chronic administration of the compounds. Research correlating toxicologic events with metabolic disposition, clearances, and profiles of metabolites is especially needed as an aid in evaluating the bioavailability of the compound and the correlation of the toxicologic event with concentration of the parent compound, its stable metabolite, or depletion of endogenous protective substances, such as glutathione.

> RECOMMENDATION 4-4: As a further aid to determining whether a toxicologic event is caused by the parent compound or a metabolite, it is recommended that toxicologic studies be performed in at least two different species or, preferably, in two different strains of the same species that metabolize the compound in markedly different ways.

Although most species differences in drug metabolism are quantitative, occasionally a unique metabolite may be formed in human tissues and not in rat tissues, or vice versa.

> RECOMMENDATION 4-5: It is recommended that studies of the metabolism of compounds be performed with human tissues to preclude the possibility that unique metabolites are not formed either in humans or in the animal model.

Although the average concentrations of a compound and its metabolites in tissues depend on many interrelated clearances and rate constants, it is important to realize that, by suitable changes in the dosage or dosage schedule, the same average concentration of a given compound or one of its metabolites may be achieved in different animal species having considerable differences in the metabolism of the substance. Thus, an animal species in which the absorption and the relative importance of the pathways of the metabolism of the substance differ rather markedly from those of most humans may still be suitable for toxicologic testing. Many biological scientists do not take full advantage of animal models because they are unfamiliar with the principles of pharmacokinetics of substances and especially of their metabolites in physiological systems. All too frequently toxicologists emphasize differences that are of trivial significance in given situations.

> RECOMMENDATION 4-6: The principles of pharmacokinetics should be incorporated in the design of toxicologic tests to make the tests more economically efficient and the interpretation and extrapolation of the results less equivocal. A better appreciation of pharmacokinetic principles leads to a better appreciation of which species differences in the disposition of substances are important and which may be ignored under given situations. It also should lead to understanding of when the incidence of disease in specific organs should depend on the route of administration of the substance.

The area of pharmacokinetics is still in its infancy. For example, the significance of measuring the relative importance of diffusional and metabolic clearances of a substance by cells is seldom appreciated. Moreover, the problems of extrapolating enzymatic data to intact cells, organs, and the entire body remain to be solved.

> RECOMMENDATION 4-7: Research is needed to obtain information on metabolic pathways and the kinetic characteristics of "drug metabolizing" enzymes from in vitro systems to determine the validity of the hypothesis that such information can be used in pharmacokinetic models to predict kinetics of disposition of specific substances in intact animals and humans.

It is now recognized that many compounds cause their carcinogenic effects or tissue lesions through the formation of chemically reactive metabolites. However, it is difficult to study the pharmacokinetics of the formation and inactivation of such metabolites. In animals, the formation of chemically reactive metabolites is usually detected by their covalent binding to DNA and protein in tissues. In humans, however, studies of this kind are usually not feasible, and thus indirect methods have been suggested. For example, it has been suggested that exposure of humans to substances that are converted to chemically reactive metabolites might be estimated by measuring the metabolite covalently bound to hemoglobin. Such a method, however, depends on the passage of the metabolite from its site of formation to hemoglobin in erythrocytes. Thus, short-lived metabolites would not be detected by this method. It is also important to realize, however, that the incidence of diseases caused by chemically reactive metabolites cannot be predicted from the amount of chemically reactive metabolite formed and covalently bound to protein.

> RECOMMENDATION 4-8: Interdisciplinary research is needed in which acute structural damage (e.g., hepatitis, nephropathy) is correlated simultaneously with the covalent bonding of the chemical or metabolite and the pattern of total metabolites. Research is essential correlating toxic effects with pharmacogenetic differences in metabolism and effects of various diets or of pretreatments that alter metabolism in the same animal cohort.

Although acute structural damage is thought to be important in the development of many lung diseases and in the promotion of cancer, the mechanisms by which chemically reactive metabolites cause cellular damage and death are incompletely understood. Indeed, it is not even clear whether different toxicants cause cellular death through a single key mechanism. One possibility is that chemically reactive metabolites interfere with intracellular ionized calcium transport.

> RECOMMENDATION 4-9: Research is needed to test the hypothesis that acute changes in the intracellular concentration of ionized calcium constitute the final common pathway mediating acute lethal injury from a variety of toxicants, including chemically reactive compounds in the environment, plasma membrane toxins, and anoxia. Documentation of the validity of the hypothesis would then focus the search for the critical target sites responsible for acute lethal injury on those organelles controlling intracellular calcium fluxes. This research documenting mechanisms of toxicity would then provide exciting new research leads into possible treatment of environmentally induced toxicity after the injury.

Most scientists agree that the scientific basis for risk assessments of newly introduced environmental chemicals is hopelessly inadequate. Moreover, the situation is not expected to improve until considerably more is known about the mechanisms by which environmental chemicals cause cancer and heart and lung disease. It is now clear, however, that most of these mechanisms are complicated and include several complex steps. Any extrapolation of incidence rates from an animal species to humans must take into account the inter- and intraspecies variations of the processes involved in each of the steps.

> RECOMMENDATION 4-10: Research is needed to develop mathematical models of carcinogenesis based on the incorporation of more biological information, including pharmacokinetic information and temporal aspects of such relevant information as formation and persistence of DNA adducts and the kinetics of promotion of carcinogenesis in various species. Validation of these mathematical models of carcinogenesis for extrapolation to man is particularly needed.

RECOMMENDATION 4-11: In order to identify the structure-activity relationships and kinetic properties of the various enzymes that metabolize carcinogenic substances and their metabolites in various species and strains of animals, the enzymes need to be isolated from tissues of animals and humans, and suitable monoclonal antibodies against them need to be developed.

RECOMMENDATION 4-12: Research is also needed to evaluate physico-organic and molecular orbital properties of chemically reactive metabolites that might be useful in predicting relative rates in combination with various nucleophiles, including protein and DNA.

There is considerable evidence that environmental substances initiate many cardiovascular and pulmonary diseases by interacting with physiological receptor sites and thereby cause abnormal physiological responses.

RECOMMENDATION 4-13: Research will continue to be needed to identify relevant receptor sites that are involved in the manifestation of cardiovascular and pulmonary diseases and to assess individual and interspecies differences in their specificity, tissue localization, and kinetic properties.

Presumably, each kind of receptor site interacts with only those compounds that have certain physicochemical and molecular orbital properties and structural features. If the structure-activity relationships of each of the receptors involved in cardiovascular and pulmonary diseases were known, it might then be possible to predict toxicities simply from the structure and molecular orbital properties of the compound. This long-term objective, however, would not be feasible unless the kinds of receptors are relatively few and their interspecies variants are limited.

RECOMMENDATION 4-14: The validity and feasibility of using theoretical and quantum chemical predictions of interactions between chemicals and receptor sites should be established. Because quantum chemical calculations currently require large-capacity computers, it may be necessary to restrict such programs to relatively few centers until the costs of computers decrease.

It is hoped that within the next several decades the scientific basis for understanding the mechanisms of environmental diseases will have grown to the extent that valid risk assessments may be made. Until that time, however, decisions to permit or prevent the introduction of new chemicals into the environment will be made with considerably less than complete confidence. In such situations, some scientists in regulatory Agencies may demand tests of the chemical in surrogate systems that will greatly increase the costs of development of new chemicals without substantially increasing our confidence in their safety. Other scientists may infer more from the results of "simple tests" than the tests are capable of providing. Congress and the public should be aware that scientists will continue to disagree on what the happy medium between these extremes should be. Whatever testing procedures are accepted, however, it seems likely that some compounds that appear to be innocuous in the tests with surrogate systems will be toxic to humans or some other beneficial living organism. It is important, therefore, that we have ways of evaluating potential toxicities of new chemicals after they have been released into the environment. There are several ways of increasing our confidence in the safety of new chemicals.

> RECOMMENDATION 4-15: To determine that a substance is not metabolized in humans along pathways that are markedly different from those in the test organisms, studies of the metabolism of the substance should be carried out in individuals shown to be exposed to the chemical either during production of the chemical or during its field trials. Occasionally, it might also be justified to study the metabolism of small doses of the substance in human volunteers, after the compound is presumed safe on the basis of laboratory animal studies and other tests.

The toxicity of many environmental chemicals was first discovered by farmers and veterinarians in domestic animals. Among these are tetrachlorodibenzodioxin, polybrominated biphenyls, ipomeanol, hexachlorobenzenes, griseofulvin, aflatoxin, and dichlorovinylcysteine.

> RECOMMENDATION 4-16: Other living organisms in the environment should be evaluated for the development of acute toxicities during field trials of the substance, and the mechanism of toxicity should be studied in those species that appear to be affected by the substance. As a part of this program, studies on the metabolism of the substance in the affected species should be performed.

> RECOMMENDATION 4-17: Accidental release of substances into the environment represents their greatest danger to human and animal health. It is now standard procedure to study the acute toxic effects of the substances in exposed humans, but the studies should be extended to exposed animals and also include studies on the metabolism of the substances. It is also important to maintain health records on the exposed individuals and control cohorts for two to three decades in order to evaluate chronic toxicities, such as cancer and chronic cardiovascular and pulmonary diseases.

CHAPTER 5. IN VIVO TOXICITY

I. OVERVIEW

The past decade has seen an extensive program of testing chemicals for toxic effects including ability to induce cancer and to damage the heart and lungs. This testing program alone is not the solution to the problem of preventing ill health in man, but existing legislation, such as the Toxic Substances Control Act (TSCA), will ensure that laboratory testing of chemicals for toxic effects will continue. Major initiatives in research are now required to develop better testing systems and to enable a better understanding of the toxic effects seen in laboratory experiments and their relevance to human health. The following areas are considered to be of immediate and fundamental importance to prevention of ill health.

The solution to problems of ill health requires contributions from a number of scientific disciplines. Furthermore, the coordinated efforts of teams of well-trained individuals, each in a separate discipline, increase the likelihood that solutions to disease problems can be found.

> RECOMMENDATION 5-1: Research in both fundamental and applied disciplines should be encouraged irrespective of their immediate application to disease states.

II. TERATOLOGY

Some proportion, which is difficult to estimate, of "functional human physiological abnormalities," including that of the cardiovascular and pulmonary systems, is the result of developmental defects. It has been estimated that a fair number of the hospital pediatric beds are occupied by children with developmental problems. Many human congenital malformations may be due to environmental agents and still others to heredity factors, i.e., gene mutations and chromosomal aberrations.

RECOMMENDATION 5-2: There exists a significant need for a validated method to rapidly and inexpensively detect substances uniquely hazardous to the conceptus. Thus, efforts to improve methods for detecting teratogens should be emphasized.

RECOMMENDATION 5-3: An extensive data base on comparative metabolism and pharmacokinetics correlated with teratogenic endpoints is needed to enhance significantly interspecies extrapolations.

There is little or no activity in this area at present; thus results on testing of teratogens in animal models are difficult to correlate with possible human effects.

RECOMMENDATION 5-4: Validated methods to detect physiological impairments versus the morphological defects, which are now the markers, are needed.

RECOMMENDATION 5-5: Methods are needed to detect additive or synergistic effects of various factors since this depicts the actual situation in humans more accurately than exposure to a single factor.

III. RESPIRATORY TRACT STUDIES

The respiratory system is a major route by which the body is exposed to the environment and, therefore, is potentially exposed to a high risk of damage. The identification of the type and extent of damage is an important prerequisite to avoiding and preventing disease. The bulk of previous research has been on the lower respiratory tract.

> RECOMMENDATION 5-6: Greater emphasis should be placed on study of of the upper respiratory tract (e.g., nasopharyngeal) by physiological, morphological, and other techniques.

> RECOMMENDATION 5-7: Greater attention should be given to the study of the physical form in which the toxic agent may be inhaled by people (vapor, aerosol, particulates, or vapor absorbed on particulates), since this often determines the sites of major impact within the respiratory system.

> RECOMMENDATION 5-8: Progression to and regression from various intermediate stages or endpoints in pulmonary and upper airway pathology should be studied further, in a manner analogous to the situation in the study of liver pathology.

> RECOMMENDATION 5-9: Studies of the mechanism by which a particular pathological process (e.g., squamous metaplasia) develops in man and animals are likely to be very helpful in assessing risk to man.

IV. TOXICOLOGIC INTERACTIONS

Toxicologic interactions of environmental agents may contribute in crucial ways to the pathogenesis of acute and chronic lung and heart disease in man. Particular attention should be addressed to combinations of agents that may interact in ways that can lead to synergistic toxicities or possibly even to entirely unexpected toxicologic phenomena. With respect to pulmonary toxicity, one good illustration of the result of such a toxicologic interaction is the florid pulmonary fibrosis caused by 70-80 percent oxygen and butylated hydroxytoluene (BHT); another is the interaction of smoking and exposure to asbestos, which causes lung cancer.

RECOMMENDATION 5-10: Emphasis on the rational exploration of toxicological interactions, based upon increasing knowledge of the metabolism and mechanisms of action of individual toxicants, should be increased.

RECOMMENDATION 5-11: The contribution of passive smoking to ill health and its interaction with other toxicants should be identified.

V. HEALTH HAZARDS ASSOCIATED WITH BIOLOGIC AGENTS

EPA is developing guidelines for the testing of biologic agents used for pest control and some current EPA research addresses one of these needs, the development of testing techniques for elucidating potential human health effects of baculoviruses. Other needs have been neglected.

The number of biologic pesticides (e.g., viruses, fungi, bacteria, protozoa) currently used is small but is expected to show a slow but steady increase over the next 5 years. In addition, biologic agents are currently being used to clean up oil spills and waste dumps. It is anticipated that the use of biologic agents for these and other purposes will increase. Health hazards of concern include infectivity to nontarget organisms, potential genetic changes to humans, immune mediated disease, and pulmonary disease. Current risk assessment activities emphasize conventional chemical agents. The development of these techniques resulted from problems recognized after extensive use of chemical agents. Early efforts to develop health assessment methods for biologic agents will minimize the hazards to humans associated with the use of biologic agents.

RECOMMENDATION 5-12: The development of techniques for the evaluation of hazards to nontarget organisms should parallel the development of the biologic agents.

RECOMMENDATION 5-13: A research resource should be established to develop techniques to monitor populations for possible harmful effects from exposure to biologic agents.

CHAPTER 6. MECHANISMS OF TOXICITY AND CARCINOGENICITY

I. OVERVIEW

The ability of many environmental pollutants to damage the genetic material of humans and animals is important because genetic damage, unless perfectly repaired, will almost certainly cause mutations. In addition, a very close relationship exists between mutagenesis (the induction of mutation) and carcinogenesis (the induction of cancer). Thus, agents in the environment that can lead to genetic damage have a very high probability of being carcinogens. It is possible that these agents may also initiate cellular processes that lead to other chronic diseases, such as atherosclerosis.

Many theories have been developed to explain the cause and uncontrolled growth of tumors. These can be grouped into two categories: changes in a cell's genetic information (somatic mutations) or alterations in the expression of genes (aberrant differentiation). Evidence can be presented to support either concept. Realizing this limitation, this panel believes that there are now sensitive methods to dissect the cell's DNA into defined molecular components and to establish unambiguously the relationship between mutation and the disease process. The rapid advances of sequencing DNA and cloning pieces of DNA by recombinant techniques have made studies on the molecular basis of mutagenesis a particularly timely topic for increased emphasis.

Carcinogenesis has been described as the progression or evolution of a normal cell to cells with altered characteristics (phenotypes) until such changes occur that allow one such cell to become invasive (malignant). A variety of physical, chemical, viral, genetic, nutritional, and other factors are known to influence one or more of the complex states during that progressive process. One major theory to organize this complex process is the initiation/promotion concept of carcinogenesis. It is derived from a wide range of experimental and epidemiological observations indicating that many cancers are derived from the exposure to agents that can induce a stable and permanent change in the genetic information of a cell (possibly mutagenesis), followed by exposure to agents or conditions that cause the selective proliferation of the initiated cell to a large clone of dysfunctional cells (i.e., promotion). Realizing that environmental pollutants may act as initiators of the cellular processes that lead to cancer, scientists in the last decade have developed a large number of tests to screen for and identify agents that damage DNA. These screening procedures, developed only after many years of basic research, are now being adequately used. This panel believes that the direction in research should shift from methods for detection of agents that cause genetic damage to research into the processes that follow the initiation step and participate in the eventual production of cancer.

The understanding of carcinogenesis requires a much more complete understanding of the myriad processes that begin immediately after genetic damage. We are woefully ignorant of the details of (1) normal replication of genetic material, (2) how cellular repair processes modify genetic damage, (3) how duplication of damaged material results in permanently encoded changes, (4) how these changes are expressed as a mutation, observable as a permanently changed cell type, and (5) how endogenous and exogenous agents promote the eventual expression of mutant cells as cancer.

RECOMMENDATION 6-1: Basic research must be supported not only to study how initiators initiate and promoters promote carcinogensis but also to study those inherent mechanisms that permit undamaged genetic material to replicate many times without error.

We must also obtain a better understanding of those processes that cause mutations and other forms of cell injury by mechanisms that do not involve direct damage in the genetic material. This requires that we determine both the mechanisms of spontaneous mutation and the ways that events outside the genetic material occasionally alter its accurate duplication.

II. BASIC MECHANISMS OF MUTAGENESIS

The relationship of mutation to malignancy is well established. In addition, there is experimental support for a role for mutagenesis in atherosclerosis and teratogenesis, and mutation may be important in other diseases involving the heart and lungs. Evidence implicating the role of mutations in at least the initiation phase of carcinogenesis is best established and includes the following: (1) a large number of known carcinogens are mutagens, (2) specific changes induced mainly in DNA correlate with transformation and tumorigenesis, and (3) in cancer-prone genetic syndromes (e.g., xeroderma pigmentosum and Bloom's syndrome), cells are hypermutable compared to cells of normal individuals. The recommendations should address the following questions:

What are the intrinsic sources of mutagenesis in cells?

This includes the determination of the normal fidelities of the polymerases, e.g., replicating enzymes, and accessory proteins involved in the replication of DNA. It also requires an assessment of the role of such other factors as gene rearrangement in mutagenesis.

What are the possible and likely events that occur when a lesion in DNA is encountered during the replication process?

To begin with, we need to understand thoroughly the detailed mechanism of normal replication, including the respective roles of specific enzyme systems and other accessory proteins. Then, using model systems, we need to learn how defined structural defects in DNA affect replication. Initially, such studies should be carried out with defined sequences of DNA and purified, well-characterized enzymes, but eventually we need to understand the events in cells. Included in this problem is the broader problem of the effect of DNA damage on control of replication initiation, a problem that ultimately relates to the dual roles of repair and replication (of lesion-containing sites) in mutagenesis.

What is the role of conditioning treatments on the biological endpoints such as mutagenesis and survival in carcinogen-treated cells?

By conditioning treatments we mean generally the exposure of the cells to low levels (subthreshold) of the carcinogenic agents prior to a challenge exposure by the same or another carcinogen. In model bacterial systems, it is well established that such "conditioning" exposures result in the induction of new pathways that enhance cell survival even at the expense of increased mutagenesis. Furthermore, one of the induced responses is the release and expression of integrated genetic material (latent viruses) from the cell genome. It is important to understand these phenomena thoroughly as well as others, such as the adaptation response of bacteria to low-level exposure to certain alkylating agents that bind to DNA. Then, we need to determine whether similar or analogous phenomena occur in human cells.

> RECOMMENDATION 6-2: We urge increased funding for basic research on the mechanism of mutagenesis--mutations that arise spontaneously as well as those that are caused by environmental pollutants. This knowledge is necessary for rational approaches to risk assessment of agents in our environment that damage cellular DNA.

III. SOMATIC CELL MUTATIONS

Several discrete, specific changes in cell heredity must accumulate in the same cell before normal cells become tumorigenic. Evidence for thinking that some or all of these changes are mutations, in a broad sense, was mentioned above. Therefore, only some evidence for the multistep nature of tumorigenesis is emphasized here because this concept is important in devising strategies for preventing malignancy. For example, when normal mammalian cells are propagated in vitro and tested for tumorigenicity, inocula of even 10^6 to 10^7 cells per site are incapable of forming tumors. As the cells proliferate, a series of preneoplastic variants appears as the result of a sequence of discrete hereditary changes in phenotype. This series includes cells that are morphologically transformed, cells that are capable of anchorage-independent growth, and cells that are tumorigenic in the nude mouse but not in immunocompetent mice. The rate at which each of these steps occurs spontaneously can be quantified in cells propagated in vitro and is similar to known rates of mutation affecting single genes of the same cells. Known carcinogenic mutagens, including ultraviolet and ionizing radiations, polycyclic hydrocarbons, and methyl-N'-nitro-N-nitrosoguanidine (MNNG), have been shown to increase the rates at which at least one or all of the steps in the preneoplastic pathway occur in cells in vitro. These preneoplastic changes can be regarded as growth control mutations.

Any factor that increases the incidence of individual kinds of growth control mutations or other cancer-causing mutations might contribute to the overall incidence of human cancer.

> RECOMMENDATION 6-3: Minimizing the somatic mutation rate by mutagen detection and elimination should be given a high priority among approaches to reducing cancer incidence. Furthermore, prevention of mutagenesis in germ cells of one generation can avert increases in the incidence of heredity factors that increase cancer risk in later generations.

There are some serious drawbacks to conventional carcinogenesis testing where tumor formation is the endpoint. The carcinogen exposures needed to induce tumor formation in experimental animals are usually extremely high in comparison to exposures that account for most environmentally induced human cancer. The means for usefully extrapolating the results of such tests to reasonable risk estimates for humans are not yet clear. Lower exposures that would ultimately increase tumor incidence during the long life span of humans might not be detectable as tumorigenic during the shorter life span of experimental rodents. However, such lesser exposures might be detectable as increases in the somatic mutation rate of experimental animals. The lower exposures that may be usable with direct testing should also make it possible to derive dose-response relationships that will make back extrapolations to low exposures more credible than such extrapolations are at present.

Determinations of induced DNA damage, adduct formation, and repair synthesis are convenient indicators of DNA damaging agents, and they are most suitable for general mutagenesis screening. Reliable ways of translating data obtained with these tests into useful risk estimates of tumor formation have not been devised. Direct testing could provide quantitative relationships between the results of convenient chemical tests and a meaningful biological endpoint, somatic mutation, when both determinations are made on the same animals. Once calibrations are defined for representative carcinogens, it might be possible to derive meaningful estimates of tumorigenic potential from data obtained from tests of any potentially carcinogenic condition with general screening methods.

Methods should be developed for quantifying in vivo somatic mutation rates in experimental animals. Such methods might be called direct testing: measuring the number of mutant cells among normal cells directly after their removal from the body. While cultivation of cells in vitro can be a part of the assay method, it is essential that the mutations that are scored occurred while the cells resided in the body of the intact organism.

Tumor formation is an inefficient endpoint for general carcinogenesis screening, and the somatic mutation rate might require less time and be a more cost-effective indicator of carcinogenic behavior. This could be learned by determining the mutagenic and tumorigenic effects of a limited number of known carcinogens in the same animals and tissues. Suitable variations of the direct testing methods might allow one to detect effects of promoters on somatic mutation rates.

> RECOMMENDATION 6-4: We urge funding of research on direct testing methods for determining in vivo somatic mutation rates in experimental animals.

> RECOMMENDATION 6-5: We also recommend support of research on direct testing methods that would be applicable to humans. The estimates of somatic mutation rates obtained with the methods could then be used to explore relations among mutation rate, retrospective cancer incidence, and prospective cancer risks in humans belonging to families with diverse risks of cancer or who occupy environments that confer different cancer risks.

It is now possible to transfer DNA from one cell to another and induce the appearance of malignancy-associated traits, such as morphological transformation and anchorage independence. In principle, this phenomenon could be used to produce recombinant DNA clones that contain the genes responsible for these traits. Such recombinant DNA clones could then be used to localize their normal and mutant counterparts in the human genome and discover how they are expressed. Ultimately, such cloned cancer-related genes might permit development of sensitive methods for detecting agents that particularly affect those genes. The interpretation of recently published experiments on DNA transfer involving cancer cell traits is not clear. The current, low efficiency of DNA transfer and the small variety of usable recipient cells restrict the exploitation of the results obtained so far.

> RECOMMENDATION 6-6: We recommend emphasis on basic research on ways of improving the efficiency of transfer of DNA and of chromatin into cells of humans and other mammals. Additional research should be done to identify types of human cells that can be used as DNA and chromatin recipients in gene transfer experiments so that ambiguity in the interpretations of experiments involving expression of cancer cell traits can be reduced to a minimum.

IV. ACCUMULATION OF DNA DAMAGE IN ANIMAL AND HUMAN CELLS

There is increasing evidence that unrepaired damage in DNA leads to mutations when the damaged DNA template is copied during DNA replication and repair. Frequently, the damage results from or represents the covalent attachment of a mutagenic chemical to a DNA base in the form of a stable adduct. Methods are at hand to detect and identify these DNA adducts after exposure of cells to high doses of carcinogens. These methods should be applied to different animals and tissues so as to relate adduct accumulation to time and concentrations of exposure to known mutagens. The goal is to determine if specific adducts correlate with cytotoxic, mutagenic, and carcinogenic changes. At the same time, measurement of DNA damage other than stable adducts should be quantified and correlated with biological changes.

Once it is known which adducts accumulate and in what tissues, it should be possible to measure the effects of particular adducts in promoting misincorporation of DNA bases when altered templates are copied by DNA polymerase enzymes in in vitro systems. Thus, it should be able to be established which adducts accumulate and what is the propensity of each for mutagenicity.

> RECOMMENDATION 6-7: Sensitive methods should be applied to measuring the accumulation of specific DNA adducts and types of DNA damage in tissues of animals exposed to graded amounts of known carcinogens.

The same methods should be directly applicable to studying damage accumulation in human tissue. Initial studies should focus on individuals having diseases with an increased proclivity towards malignancy and individuals naturally exposed to high doses of known mutagens and carcinogens. To evaluate these data, we must know the background level of adducts and unrepaired regions of damaged DNA. With this information, we can relate damage to DNA by environmental agents to the biological effects that result from this damage.

Of particular interest will be the quantitation of different adducts and types of DNA damage in various human tissues. It is important to understand why different types of cancer are tissue specific even in individuals with diseases in which DNA repair is diminished in multiple if not all cell types. In addition, human tissue removed at death or at elective surgery can be cultured in a morphological state for periods of months. Such tissue can be exposed directly to model carcinogens for damage or repair studies.

> RECOMMENDATION 6-8: Similar methods should be developed for studying human cells, particularly in individuals with diseases that have deficiencies in DNA repair.

V. THE ROLE OF PROMOTION IN THE CARCINOGENIC PROCESS

The observations that led to the concept of tumor promotion are well documented. Agents and conditions that can lead to the selective proliferation of an initiated cell to a tumor are not necessarily mutagenic. Various molecular, biochemical, and biological responses have been associated with chemicals that can be tumor promoters. Among these promoter-induced responses in cells are (1) alteration of the regulation of proliferation or differentiation of cells; (2) change in membranes; (3) induction of enzyme activity and synthesis; and (4) inhibition of cell to cell communication processes. Surgery, wounding, cytotoxicity due to mutagenic and nonmutagenic chemicals, normal growth factors and hormones, and environmental chemicals are all documented modes of tumor promotion.

Clearly, we do not have basic knowledge concerning the molecular mechanisms that allow an initiated cell to grow into a tumor. Although a large number of phenomenological studies are presently being supported, there should be increased emphasis on the study of the molecular mechanisms of tumor promotion. Indeed, if the initiation/promotion model is correct for human carcinogenesis, exposure to mutagens, as bad as it is, might be insufficient to cause cancer. Subsequent and chronic exposure to nonmutagenic but promoting chemicals might be as important in the environmental component of carcinogenesis as are mutagens.

Many environmental, dietary, drug, and naturally occurring chemicals, such as croton oil, components of cigarette smoke, asbestos, DDT, PCB, saccharin, phenobarbital, and bile salts, are promoters of various organ- and species-specific tumors. These chemicals are all negative in various mutation and DNA damage assays. How all these widely different chemicals act as promoters and how they might act similarly or differently from surgery, cytotoxicity, or natural growth factors are fundamental scientific problems that need to be explored.

Since cancers are derived from cells capable of proliferating (terminally differentiated cells do not give rise to tumors), it is suspected that all the modes of promotion allow an initiated stem cell in an organ to escape the influence of the surrounding tissue that suppresses their growth. Surgery and cell killing could allow the surviving initiated cells to replicate the tissue during the wounding or regeneration process, giving rise to clones of dysfunctional cells. During that replication process of the initiated cell, other genetic and epigenetic events could occur, ultimately giving a cell the selective advantage to grow in an unregulated fashion. Cytotoxicity, due either to chemicals that can induce DNA damage leading to viable and lethal mutations or to nonmutagenic chemicals that kill cells, would allow some of the surviving cells, if mutated by the cytotoxic mutagen or by a previous mutagen, to be promoted. In other words, cytotoxicity can be an indirect promoter by allowing surviving mutated cells to grow into a clone of dysfunctional cells during the regeneration of tissue.

One recent hypothesis on the mechanism of tumor promotion is that tumor promoters interfere with the interaction of an initiated cell with its neighboring normal cell. Evidence supporting the role of cell to cell communication in tumor promotion includes the following observations: (1) many tumor promoters block communication between physically contacting cells; (2) some known tumor promoters cause gap-junctions (physical structures on cell membranes that allow cells to transfer molecules) to disappear; (3) tumor cells do not communicate well with each other (normal cells are contact inhibited but cancer cells are not); and (4) regenerating liver (a mode of promotion) is associated with the disappearance of gap-junctions (after the liver is regenerated, gap-junctions reappear). Additional research to explore other possible hypotheses must be encouraged.

> RECOMMENDATION 6-9: Funding should be provided for studying the basic molecular mechanism of tumor promotion, including support for research that would allow examination of the molecular basis for species and tissue specificity of tumor promoters, and funding is needed to study the cellular basis for tumor promotion, especially in the area of the basic mechanisms of cell to cell communication.

As in the case for screening for mutagens, we must have some indication of how promoters act before we can design short-term assays to detect potential tumor promoters. In the case of chemical tumor promoters, we do not yet know how they act; however, we do know that they seem to be tissue and species specific. Consequently, much more fundamental basic research on the mechanisms of tumor promoters must be supported before in vitro assays can be used to detect potential tumor promoters.

> RECOMMENDATION 6-10: Based on the knowledge obtained from implementing recommendation 6-9, simple screening assays should be developed to measure cellular effects of tumor promoters that are relevant to human diseases.

The above areas seem to us to be the most important for understanding the mechanism of mutagenicity/toxicity. Only by studying basic mechanisms will it be possible to devise approaches that allow us to obtain an adequate risk assessment of environmental pollutants. The recent discovery of methods to sequence DNA and to clone DNA by recombinant techniques should be applied to studying DNA damage by environmental agents. Directed or targeted research in this area probably will not solve these problems, because innovative and original approaches are needed. Therefore, it is important to let the scientific community know that there is support for original basic experiments aimed at understanding the mechanism of mutagenicity, promotion, and toxicity.

Appendix

KEYNOTE ADDRESSES

INTRODUCTORY REMARKS

Morris I. Kelsey, Ph.D.
National Cancer Institute

Good evening, and welcome to the introductory session for the Workshop on Exposure, Metabolism, and Mechanisms of Toxicity.

For those of you who may be wondering why we were delaying the start of our session, we were waiting for one of our speakers, Congressman Martin, who probably has been detained with all of the traffic coming out of Washington, today being a very special day. However, the consensus--at least I hope there is a consensus--is that perhaps we should proceed anyway and begin. Hopefully he will be here before we have completed our activities tonight.

There are a number of you here whom I haven't met yet. For those of you whom I haven't met, my name is Morris Kelsey and I am the Chairman of this program. I hope to meet each and every one of you throughout the next few days.

The best way in which I thought I might begin some introductory remarks is to pose a few questions; namely, why are we all here tonight, and for those of you who are invited participants at the Workshop, what are we supposed to accomplish? I think that before I can begin to answer those questions, and hopefully address those concerns that some of you might have, I thought perhaps I would give you some background as to this Workshop that we're having this week.

The activities that we are going to be engaged in for the next few days are very necessary in order that we may provide important information in the form of research needs to the Interagency Task Force on

Environmental Cancer and Heart and Lung Disease. Hereafter I will refer to that interagency group as the Task Force.

Now by way of history, the Task Force was established by the Clean Air Act Amendments of 1977 in order to focus efforts by the United States Environmental Protection Agency and other Federal Agencies on the development of coordinated comprehensive Federal research programs, and to develop strategies for the reduction of the incidence and risks of environmentally induced cancer and heart and lung disease.

The members of this Task Force are as follows: the Environmental Protection Agency is chair Agency in this effort. Other Agencies involved are the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute for Occupational Safety and Health; the National Institute of Environmental Health Sciences; the National Center for Health Statistics; the Centers for Disease Control; and, more recently, the Food and Drug Administration.

Under the terms of these activities mandated through the Clean Air Act, the Task Force is required to report annually to Congress on its progress and problems, and that's why I can now get back to the original question which I threw out to the audience.

Tonight, as you can tell from the program, we have assembled a distinguished group of scientists, and these scientists will present this evening some overviews regarding the status of our knowledge on the relationships between environmental pollution and these various diseases, namely, cancer and heart and lung disease.

Over the next few days, we will attempt (and succeed, I might add) in looking at this complex problem of environmentally induced cancer and heart and lung disease, and assessing where we are. More importantly, and this is where we really have to address our attention, we have to draft research needs and future directions for research in these areas. These research priorities will be achieved through a consensus reached in the respective subgroups, and eventually Plenary Sessions which we have scheduled.

These needs will then be submitted to the appropriate committees of the Task Force for their consideration as research recommendations to Congress and will be included in the Task Force Annual Report to Congress, which will come out some time in the summer of this year. For those of you who may be interested in the past activities of the Task Force, we do have copies of the Third Annual Report to Congress at the registration desk.

In terms of the structure of this workshop, tonight's session is really the only one that will contain formal presentations. This is going to be a meeting of active participation by all of the invited attendees in reviewing position papers which have been submitted by most of you prior to our meeting here today. These papers will be sources for drafting recommendations or research needs, and your group sessions will discuss a number of wide-ranging topics.

These topics include problems in gaining access to Federal data systems for epidemiological research; monitoring of human exposure in the workplace or general environment through improved analytical techniques; new approaches that can be used to assess human exposure to pollutants in various environmental media; the importance of understanding detailed mechanisms of activation and detoxification of environmental pollutants and the potential effects on human health, particularly with respect to comparing animal and human data; details concerning the modulation of toxicity which results from the interaction of environmental pollutants with critical cellular macromolecules; and the consequences of the interactions to the host.

Here we have an opportunity to examine the interactions of these environmental pollutants with such macromolecules as DNA; what happens as a result of that, such as repair, replicative processes, and effects on gene expression, are perhaps common toxicological events in cancer and heart and lung disease.

Indeed, the next few days should be exciting, challenging, and productive as we attempt to reach our main objective in drafting these research needs in all of these areas.

Finally, I would like to express my thanks publicly to a number of people, some of whom I won't have time to mention todav, but there are certain individuals whose optimism in achieving our goals here was really a necessary ingredient in order that this Workshop this evening could take place.

These individuals include Dr. Vilma Hunt, who is the Chairperson of our Working Group in the Task Force, and the various chairpersons and cochairpersons who will be leading the various subgroup sessions, including Drs. Tom Mason and Paul Leaverton in the exposure epidemiology area; Drs. Herman Kraybill and Lance Wallace in the exposure quantification area; Drs. Jim Gillette, Larry Hart, and Elizabeth Weisburger, metabolism; and Dr. Larry Loeb, mechanisms of toxicity.

Last, but by no means least, a person with whom I'm sure you are probably more familiar, Ms. Peggy Young of GEOMET, who has worked so hard in the last 9 months in my association with the Task Force, and I know she's worked longer than that, in arranging all of the logistics and the painful nitty-gritty of organizing a workshop of this type.

PROBLEMS IN INVESTIGATING THE ROLE OF ENVIRONMENTAL FACTORS IN HUMAN DISEASE

Robert S. Gordon, Jr., M.D.
National Institutes of Health

What methodologies are available to us in investigating environmental causes of human disease? They can be counted on relatively few fingers if you use broad terms. One that we might think about for a few minutes is animal models. A number of you here are experts in that field, and I believe that will be one of the topics for discussion later in the workshop. Animal models can be a very useful guide. They certainly can help develop tentative answers to many problems. But there are important shortcomings in research on animal models.

For one, in any kind of manageable experiment, one must have a higher morbid event rate in the experimental animal population than what we normally observe in our human population. As a result of an experimental setup where we must strive for a higher event rate, we have to extrapolate the results of the animal experiment to the human situation, and this always involves an assumption of some dose-response relationship that ordinarily cannot be proven in the animal study.

A second shortcoming in animal experimentation is that one usually cannot simulate the genetic and other human polymorphisms that define subpopulations of unusual susceptibility. In the human population we are often interested in the tail of the distribution curve, whereas in the laboratory we are looking at animal experiments in the middle of the distribution curve, where the cause/effect relationships are not always the same.

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Finally, with animal experiments, one can rarely simulate the psychosocial and behavioral factors that may very well interact with environmental factors as causative agents in disease. Therefore, although you can do a lot with animals, you ordinarily cannot answer the $64,000 question.

What can we do with human experimentation? Those of us who have a background in clinical research are very familiar with human experimentation on newly developed cures of disease. But in investigating the cause of disease, we obviously have a very important ethical limitation. We cannot deliberately cause human disease, certainly not irreversible disease, in an experimental situation. Short of inducing irreversible and serious disease, there are some experiments that can properly be done with man, under adequate safeguards.

We can investigate metabolic pathways, using molecules that are related to suspected serious toxins but are not themselves as toxic, or we can even use trace amounts of some of the most dangerous chemicals as long as they are heavily labeled with radioactivity and administered in almost infinitesimal quantities.

We can develop analytic methods to apply to human body fluids and other tissues to measure the exposure or to measure the body burden of exogenous chemicals. I notice that is another topic on your workshop agenda. We can also do research on other methods to document and to quantify exposure.

Finally, though, we exhaust what we can do in preliminary fashion using these varied methodologies. Then we are forced to adopt the epidemiologic approach and the so-called "quasi-experimental" situation in which we take scientific advantage of human exposures that have already occurred or are being caused to occur for reasons other than our scientific interest. We try to measure such exposures and to relate outcomes to the exposure. We cannot control or produce the situation, but given an existing situation, we can do our utmost to derive useful information from studying it.

Actually, such epidemiologic work is the principal reason for believing that we have a problem with environmental cancer and heart and lung disease. I do not intend to review this epidemiologic evidence, as it will be discussed by other speakers on the panel tonight. But before turning the podium over to them, I would like to discuss some of the difficulties that beset the epidemiologist trying to study the problems of environmentally induced chronic disease.

One of the greatest strengths of epidemiology is in testing hypotheses. However for formulating hypotheses, it is sometimes a clumsy, cumbersome, expensive, and ineffective method. The need to rely on other disciplines for hypothesis generation is one difficulty the epidemiologist faces, and this is where plausible hypotheses derived from animal experimentation and other methods that I have just mentioned can be so valuable.

A second obvious difficulty, which we do not need to dwell on tonight, is that small relative risks, those below about 1.2 or 1.3, are essentially unmeasurable by epidemiologic methods. The confidence limits always seem to include the relative risk of 1, and the final conclusion has to be that there is only a trend, not a statistically significant occurrence. The commoner, and therefore, more important the disease and the higher the background rate, the harder it may be to measure an excess. An excess which is extraordinarily important because it may represent in absolute terms a very large burden of human disease may disappear into a very small relative risk because of the large denominator.

Thus, in the case of a rare and therefore relatively unimportant disease like hepatic angiosarcoma induced by vinyl chloride, just a few cases suffice to identify the cause. But when it comes to heart disease, which is responsible for almost half the deaths in this country, we struggle to find etiologic factors that may affect thousands of people every year.

Another difficulty stems from the long latent period that characterizes all of the diseases that this conference is concerned with. If the latent period between cause and effect is long, there is obviously greater opportunity for extraneous correlated and confounding variables to creep into the equation. Factors that may in no way be related to the etiology of the disease still may show an association that has to be dissected out, often with great difficulty.

I would like to discuss in more detail two other related problems of public policy that affect epidemiologic research. I want to bring to your attention some of the deliberations of other groups that have considered these issues because of the relation of environmental factors other than chemical pollutants to the cause of human disease. These two problems, which I think may be related, are, on the one hand, overexpectation and, on the other hand, legal impediments.

The public and their elected representatives in Congress seem to me continually to underestimate the difficulties in doing epidemiologic research and to overestimate the productivity. Therefore, they come to this attitude of overexpectation.

Let me just cite a few examples. Consider diet and nutrition in relation to disease. There are many reasons to believe that lifetime dietary habits are important determinants of health status. But these relationships are very difficult to study, and we are only beginning to establish a few basic ones. The public has been confused, and the Congress has been calling for acceleration of programs in this field.

For several years, until very recently, the Congress had, as you know, the Select Committee on Nutrition and Human Disease headed by ex-Senator McGovern. The committee felt, a couple of years ago, that there was sufficient evidence to publish a rather complete and explicit set of dietary goals for the American population. I think those of us who are in the scientific research field have, to say the least, taken Senator McGovern's recommendations with a grain of salt. The evidence, though suggestive in a number of cases, certainly is not complete, and to adopt any such specific set of dietary recommendations would produce major economic changes to the advantages of many people. The "incredible edible egg," for example, is very much on the defensive against the recommendations of Senator McGovern's committee and of some others who have espoused the idea that dietary cholesterol is important in causing heart disease. A great deal of controversy has resulted from such uncertainty, as well as concern that those of us doing research are not doing enough to answer the obvious questions about what we should and should not eat.

Low-level chronic exposure to ionizing radiation has been another political football over the last several years. Where exposures to ionizing radiation have been higher, as in populations that suffered the effects of the atomic bombs in Japan in 1944, among U.S. military personnel who were exposed to atomic bomb tests in Nevada, and among those who experience occupational and medical exposures in the past, before the danger was recognized, health effects are very clear. There is no doubt that ionizing radiation is damaging to people when a sufficient dose is received. But what do we know about chronic exposure to very low levels? Again, Congress exemplifies the public feeling that we ought to find out, and that we ought to do it promptly.

Let me cite just a few references. Public Law 95-601, passed in 1978, requires the Nuclear Regulatory Commission, the Environmental Protection Agency, and the Department of Health and Human Services to do epidemiologic research on the health effects of low-level ionizing radiation. A bill, S-1865, introduced in 1979 but not passed, would have required the Public Health Service to conduct a comprehensive assessment of the adverse health effects resulting from the Atomic Weapons Test Program since January 1, 1951. HR-6745, the same year, would have provided that, on the basis of epidemiologic data and other scientific information, the Administrator (referring to EPA) shall establish the most likely statistical relation between a given exposure and the consequent harmful effects therefrom.

Other congressional language, again from a bill, would have asked HHS "to determine whether there is or may be a relationship between exposure of such individuals to nuclear radiation during such period and any abnormal health symptoms currently exhibited by individuals." This referred to the U.S. military personnel who entered Japan not long after the explosion of the atomic bombs but whose actual recorded radiation exposure was miniscule.

Let us examine some of the expectations of Congress about research on the health effects of chemical exposure. PL 95-623 demands a study of the present and future health costs of pollution and other environmental conditions resulting from human activity. Further, it asks epidemiologic research to identify the environmental conditions that are responsible for causing or aggravating human diseases, and specifically to determine whether cancer, birth defects, genetic damage, emphysema, asthma, bronchitis, heart disease, stroke, and mental illness represent such diseases or effects. I could go on citing examples. There are enough of them that I think one can easily detect a widespread feeling that whatever your problem is, you should get an epidemiologist to straighten it out for you.

On the other hand, perhaps related to this attitude of overexpectation, there seems to be an attitude that the epidemiologist, brave fellow that he is, can fight off the enemy with one or one-and-a-half hands tied behind his back. Whereas we find our elected representatives urging us to tackle all of these important problems, we also find a series of legislative actions that make it quite difficult to get access to the information that may be required. The problem is most serious when we require access to information collected in the past, at a time when people, through ignorance, were not so conscientiously avoiding the hazards that we are concerned with. I am reminded of the famous quote from George Santayana, "Those who disregard the past are bound to repeat it." What worse fate could we have? There are laws that deny researchers access to useful information contained in Federal files. I'll just touch on a few examples here because one of your workshops will examine the issue in more detail.

The provisions of the Tax Reform Act of 1976 were motivated by quite real abuses. For example, in the past it was possible for commercial promoters to get from the Internal Revenue Service the names and addresses of people who fell within certain tax brackets and who lived in certain geographic areas, an obvious target for advertising campaigns and junk mail. I think Congress quite wisely felt this that was an abuse of the internal revenue system, and passed a law to stop it. At the same time, they made it impossible for the Internal Revenue Service to tell a public health investigator whether a given person was alive, as evidenced by his filing tax returns, and where he lived.

An investigator now has to pay Equifax or another such agency $100 or so per name to have a cohort traced, instead of the 10 cents per name that it used to cost to run the computer files at IRS to get the most recent mailing addresses for a list of people. That is a real difference, a matter of a thousand-fold in the cost of locating people whose current addresses you may need for very valuable research.

The Privacy Act of 1974 has not been quite as serious a deterrent because it has more loopholes, including a provision for "Routine Use," but it still denies access to Federal files to investigators who, for one reason or another, can't qualify under routine use.

The Veterans Administration has a confidentiality statute that prohibits the release of medical or other disability, pension, or death information to researchers unless they are within the Veterans Administration. The VA itself has recently proposed a modification of that law that would give the Administrator of the VA discretion to make this information available to researchers (in cases the Administrator felt were worthy), but that law has not yet been changed.

Several proposals were submitted to Congress recently that Congress did not have time to act on during the past session. These are still on the record as recommendations, primarily contained in the report of the Privacy Protection Study Commission. I recommend this report to you. It contains a great deal of interest, including specific directions for how to get your name off junk mailing lists. There are also a number of recommendations that I hope will be revived during the present session of Congress.

Specifically, there are recommendations dealing with the privacy of medical records that would allow medical record information to be released at any time with the consent of the person to whom the record applies. Without such consent, information could be provided for bona fide investigations which in general would have to satisfy two criteria. First, the investigation would have to have been reviewed and approved by an institutional review board. Second, the investigational plan would have to be such that the individually identifiable information in the medical record would be held in confidence by the investigators and would never be published.

There has been a proposal for research record privacy that would be very advantageous because it would give an investigator a legally sound basis for assuring a respondent that he would hold in confidence information that was given to him for a public health research project. That cannot be done now. Such records can be taken from an investigator under subpoena.

There is a third provision, with which I am less familiar, but which would seem to be very advantageous for research. It would permit the exchange between specific Federal statistical enclaves of confidential information that has been collected for specific purposes. As long as it did not leave the confidential enclave, information collected for one purpose could be used for another legitimate purpose without the expense and nuisance of duplicate collection.

In relation to this, I refer you to the editorial by Dr. Gilbert Beebe,* which is part of the handout material that I have brought tonight. In many other countries, all governmentally collected statistical information is held by one statistical agency; therefore, cross-linkage between different records can be effectively carried out when there is a legitimate purpose for doing so. In our Government, with its system of checks and balances, many different Agencies hold information for a specific purpose, and in most cases they are barred from exchanging it even between or among themselves. Thus, records that might make it relatively easy, straightforward, and inexpensive to carry out useful investigations become inaccessible.

In summary, I believe we face a need to develop among our population wide recognition and public acceptance of the fact that, just as an individual patient has to be frank with his physician for diagnosis and cure of a disease, so society has to be open and frank with public health investigators so that environmental causes of disease can be identified and controlled. If we can get that idea widely accepted and made the basis of laws and regulations, we probably will find ourselves moving much more rapidly toward the answer to many of the problems that this Task Force is addressing.

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* Am. J. Public Health, vol. 70, pp. 1246-1248, Dec. 1980.

I would like to close by relaying to you the greetings and best wishes of Dr. Donald Fredrickson, the Director of NIH, who wished he could have been here himself. He and all of us hope that this will be a successful conference and that some good findings and recommendations will come out of it.

ENVIRONMENTAL AGENTS AND RESPIRATORY EFFECTS

Jean French, Ph.D.
Centers for Disease Control

The major research efforts among environmental health researchers for the past few years have been devoted largely to carcinogenicity, teratogenicity, and mutagenicity, with relatively little attention given to other disease processes such as acute and chronic lung disease. Yet the respiratory system bears the greatest insult from exposures to toxic agents found in the ambient air, in the occupational setting, and in the indoor environment. The consequences of such toxic exposures from a clinical and pathological standpoint are dependent upon the physical and chemical properties of the agent, the duration and intensity of the exposure, and the host susceptibility.

The agents may be inhaled in the form of a particle or a vapor, or in a combination of these states. We know that particles of 5 microns or less in diameter are capable of reaching the deep lung, and those that are less than 1 micron in diameter have the highest probability of deposition in the deep lung. It is also important to note that the capacity of the lung to clear such particles is highly efficient, and, under ordinary circumstances, the lung can eliminate all particles less than 5 microns in diameter if the mechanism is not overwhelmed. However, it has been estimated that when air concentrations approximate 1,000 particles per cubic centimeter, only 90 percent of particles 5 microns or less in size are cleared.

The fate of these substances once they reach the deep lung is dependent upon the physical and chemical properties of the agent, whether it

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is reactive, and how soluble it is. We know that the more highly soluble reactive substances can result in acute inflammatory reactions, very often leading to pulmonary edema.

The response of the respiratory system to such insults may be either acute or chronic. Some of the acute effects include cough, bronchoconstriction, increased mucus secretion, intense inflammatory reaction, and loss of ciliary function. Chronic effects may include mucous gland hyperplasia, goblet cell metaplasia, chronic inflammation and ciliary dysfunction, changes in the surface area of the alveoli, and connective changes with subsequent loss of alveolar form. And, of course, we know that some of these things may result in neoplasia.

Tonight I would like to dwell on some agents found in the ambient air that are known to cause adverse health effects in the workplace and in the indoor environment.

Ozone, which is a major constituent in smog, is a very severe respiratory irritant that can cause increased susceptibility to acute respiratory infections and alter pulmonary functions in adults.

Studies in laboratory animals and in epidemiology have shown that nitrogen dioxide, which is another very common pollutant found in ambient air, exerts its primary effect on the lung. Nitrogen dioxide can cause several categories of effects. In very high doses it can cause an acute fatal type of reaction, usually due to pulmonary edema. Lower doses over a prolonged period of time can cause loss of pulmonary function. This loss of function can contribute to increased susceptibility to acute respiratory infection and can also cause biological and structural changes which are compatible with chronic respiratory disease.

The pure gas sulfur dioxide, another common ambient pollutant, is a mild respiratory irritant which is absorbed in the upper airway and manifests its effect largely through increased bronchoconstriction and increased airway resistance. However, the chemical transformation products of sulfur dioxide, namely, sulfuric acid and certain metallic sulfates, are far more irritating than the sulfur dioxide gas alone.

It has been difficult to study the effects in humans of exposure to sulfur dioxide and total suspended particulates because all too often these two pollutants occur simultaneously. However, the eruption of Mount St. Helens provided a unique research opportunity to study the effect of exposure to high levels of crustal particulates in the absence of high levels of sulfur dioxide.

The Communicable Disease Center set up a surveillance system following the three major eruptions of Mount St. Helens, and that surveillance system showed increased emergency room and hospital admissions for upper airway disease in the heavily affected areas. The data base accumulated in this research will be of value because such crustal particulates do make up a large portion of suspended particulates in some parts of the United States. CDC also hopes to participate in a study of a volcano in Nicaragua which is leading to exposure to high levels of sulfur dioxide and low levels of total suspended particulates.

Although we have qualitative information about the respiratory effects of pollutants found in the ambient air, at the present time we do not have an adequate data base of the actual exposure levels that cause some of these effects. This is a very critical research area.

As you know, the Clean Air Act is coming up for review before Congress this year, and there is a strong possibility that this Act may be greatly weakened. This then puts a burden on the research community to identify adverse health effects associated with such exposures so that appropriate steps may be taken to protect the public health.

In the occupational setting, it is estimated that at least half of all occupationally related diseases are respiratory in nature. Such agents as asbestos, beryllium, cotton dust, sulfuric acid, sulfur dioxide, toluene, silica, phosgene, phosphoric acid, nitric acid, and a multiplicity of other agents commonly found in the workplace are known respiratory irritants that can cause respiratory disease. It is estimated that in the coal industry alone, $1 billion a year is spent in disability payments for people with black lung disease. Presently compensation is underway to reimburse people who have had exposures to asbestos and to cotton dust. If we can find factors of causation of respiratory disease and follow up with appropriate modification of industrial processes, we really could have a profound effect on health care costs.

An emergency problem area, particularly as related to the respiratory system, is that of indoor air pollution. We have found that energy conservation measures have led to very poor air exchange in homes and in office buildings. This has permitted a buildup of both chemical and biological agents in these settings, very often resulting in respiratory symptoms.

CDC, both the Epidemiology Branch in Atlanta and our sister agency, CDC/NIOSH, have received a multiplicity of complaints from people having symptoms related to exposures in buildings. We have investigated some of these situations and very often find people with symptoms of respiratory irritation and nasal congestion. The symptoms start when they enter the building to begin their work and disappear when they leave the building after they have completed their workday. However, if the exposures continue, we find that the symptoms persist.

In a recent investigation, we found that residue of detergent was left in a carpet after the carpet was shampooed with a detergent that was not properly diluted. This resulted in symptoms of respiratory irritation in all of the people working in one building, in all of the adult staff, and many of the children in a daycare nursery.

The investigation did incriminate the particular agent in the shampoo, which was sodium dodecyl sulfate. In many of these situations, however, we have not been able to identify a single agent, but rather have found an air system with an inadequate filter and a very low air exchange rate, which then permits agents to accumulate and to exert an effect on populations that inhabit these places.

Indoor air pollution is becoming a very real problem. I hope that indoor air pollution, particularly in the light of energy conservation and some of the architectural methodologies that are being used, will deserve some attention in this Workshop.

Another area where we are seeing problems is exposures to toxic waste sites. A dramatic example of this was in a community in Globe, Arizona, where 50 mobile homes were located on a site that was previously an abandoned asbestos mill.

The asbestos mill tailings were used in grading the land. On measuring the soil outside of these mobile homes we found 5 to 60 percent asbestos fibers in the soil, and in the indoor environments of these mobile homes, we found levels of asbestos fibers which far exceeded the NIOSH 8-hour time-weighted average. This prompted us to recommend that this community be relocated and the site be cleaned. We also have collected information which will permit us to follow these people over time to see if there are any long-term effects and lung changes from the asbestos exposure.

We have also seen a multiplicity of situations, largely resulting in respiratory complaints, from spills and from other chemical emergencies such as the Elizabeth, New Jersey, fire. There are increasing acute emergency episodes which are contributing to chemical exposures that lead to increased respiratory problems.

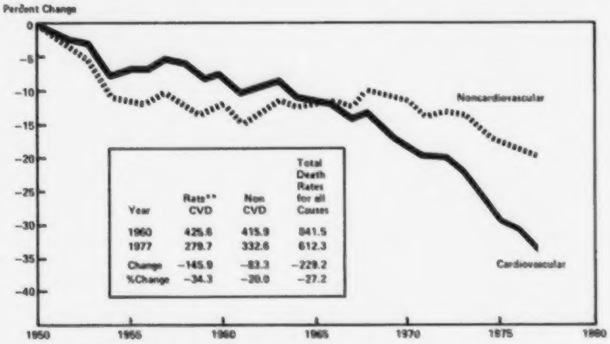
Acute and chronic respiratory disease deserves attention in this Workshop, particularly in light of the fact that it manifests itself after a much shorter exposure time. It affects disability and influences the quality of life.

ENVIRONMENTAL FACTORS AND HEART DISEASE

Manning Feinleib, M.D., Dr.P.H.
National Heart, Lung, and Blood Institute

Ladies and gentlemen, I would like to spend a few minutes telling you about the changes in cardiovascular mortality that have been occurring during the last few years, and from that go on to a broad overview of some of the problems and opportunities for research in environmental factors. I will conclude with some of the problems we're facing in trying to pursue this research effectively.

When we talk about environmental factors in cancer, heart, and lung disease, we sometimes get the image of a rampant epidemic that is going to devastate our nation due to an increasing degree of pollution and exposure to environmental substances. In terms of mortality, we hardly have an epidemic. In fact, during the last 30 years, we have made tremendous progress in reducing the overall mortality in this country, and especially the mortality due to cardiovascular diseases. Since 1950, there has been over a 30 percent decline in the age-adjusted mortality rates from cardiovascular disease, and about a 20 percent decline in the mortality from all other causes (Figure 1).



Year	Rates** CVD	Non CVD	Total Death Rates for all Causes
1950	425.6	415.9	841.5
1977	279.7	332.6	612.3
Change	-145.9	-83.3	-229.2
%Change	-34.3	-20.0	-27.2

* Age adjusted to the U.S. Population, 1940
** Excluding Congenital Heart Disease

Figure 1. Percent Decline in Death Rates* Since 1950 for Cardiovascular and Noncardiovascular Diseases

With regard to ischemic heart disease or heart attacks, which is the single leading cause of death in the United States, we have had a very interesting epidemiological pattern. Since the disease was first reported in the 1940's up until the mid-1960's, there was a steadily increasing trend in the mortality from this disease both for men and women, and for whites and blacks. Then in the mid-1960's, with some exaggeration of the trend due to the change in the International Code in 1968, there was a shift in this trend. After 1968 there has occurred a remarkable decline in this disease incidence, even more precipitous than the rise during the preceding years (Figure 2).

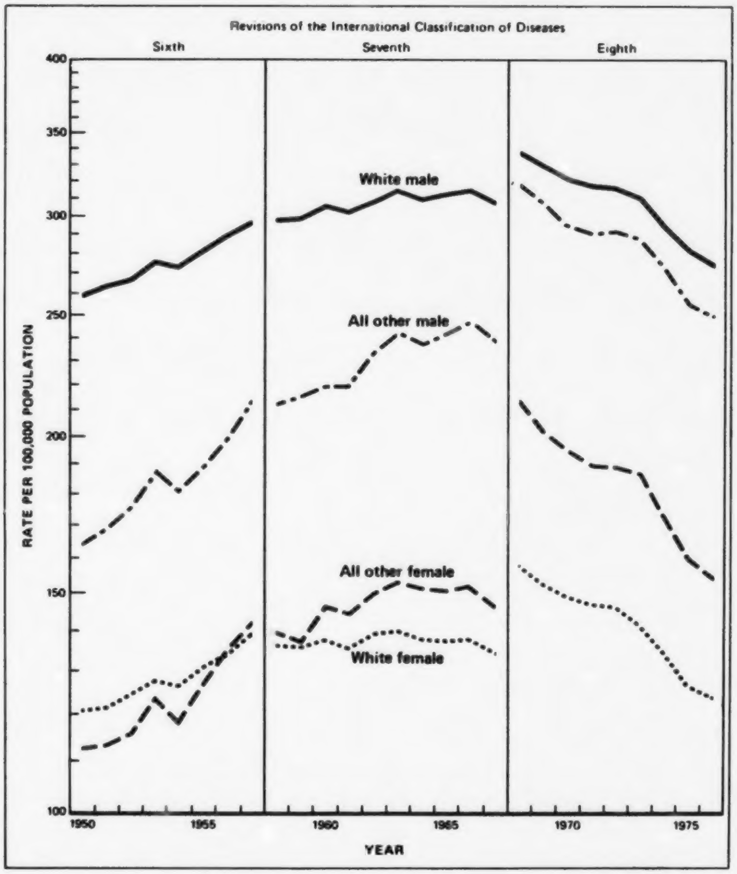
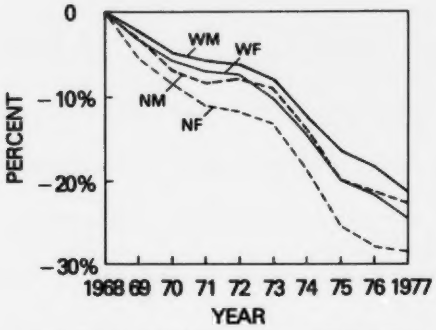


Figure 2. Age-adjusted Death Rates for Ischemic Heart Diseases, by Color and Sex: U.S., 1950-76

This decline has amounted to between 20 and 30 percent in the 10-year interval from 1968 to 1977 and has occurred to about the same degree in white men, white women, nonwhite men, and nonwhite women (Figure 3). Yet such a decline can hardly be attributed to lowering of exposure to environmental factors, environmental toxins, environmental pollution. Moreover, this trend has not been similarly experienced around the world. There are only a few countries which have shown any signs of decline in ischemic heart disease mortality.



SOURCE: DATA FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Figure 3. Percent Decline Since 1968 in Age-Adjusted Coronary Heart Disease Death Rate by Color and Sex: U.S., 1968-77

In Figure 4 is shown the relation of the 1975 death rate from ischemic heart disease in men aged 55 to 64 in various countries relative to the 1970 death rate. If there had been no change during that 5-year period, the points would lie on the solid line. As you see, the vast majority of the points do lie on or near that line. The dashed line in this figure represents a 10 percent decline in the 5-year period, or a decline of 2 percent per year.

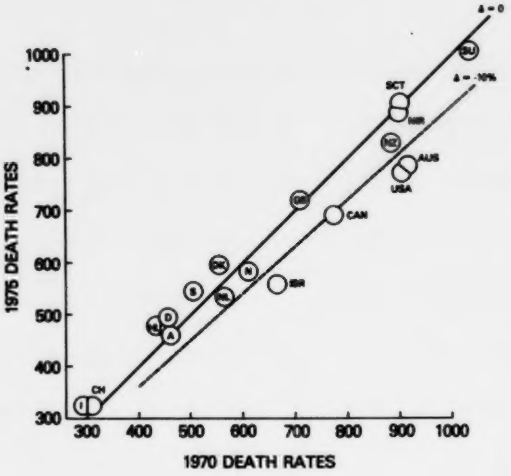


Figure 4. Death Rates Per 100,000 for Coronary Heart Disease: Males, Aged 56-64

There are are only four countries in the world that have achieved or exceeded a 10 percent decline during that period: the United States, Australia, Canada, and Israel. More recent data show that a few countries, Scandinavia especially, are starting to show a decline, but the U.S. is still leading all the other countries in this reversal of trends in heart disease mortality.

Figure 5 poses an important question. Can we identify the factors causing the decline in coronary heart disease and measure the contributions to the decline? At the National Heart, Lung, and Blood Institute, we held a meeting of national and international experts about 2 years ago that addressed a wide variety of questions and issues pertaining to this decline. Whether the decline was really a true statistical trend or rather an artifact through errors in statistical recording, coding, or other factors was a key issue. The conference concluded that the decline definitely was real and, in fact, has been continuing. The experts looked at a variety of factors. Broadly speaking, these factors were broken down into two classes:

(1) those related to improved medical care (a lowering of the fatalities from heart disease perhaps not due to any real drop in the incidence of heart disease), and (2) factors related to improvements in what we call the risk factors that might lead to heart attacks, thereby reducing the actual incidence of heart attacks. These factors included changes in diet, treatment of hypertension, lowering of cholesterol levels, less smoking, and a variety of other personal risk factors which might contribute to heart disease.

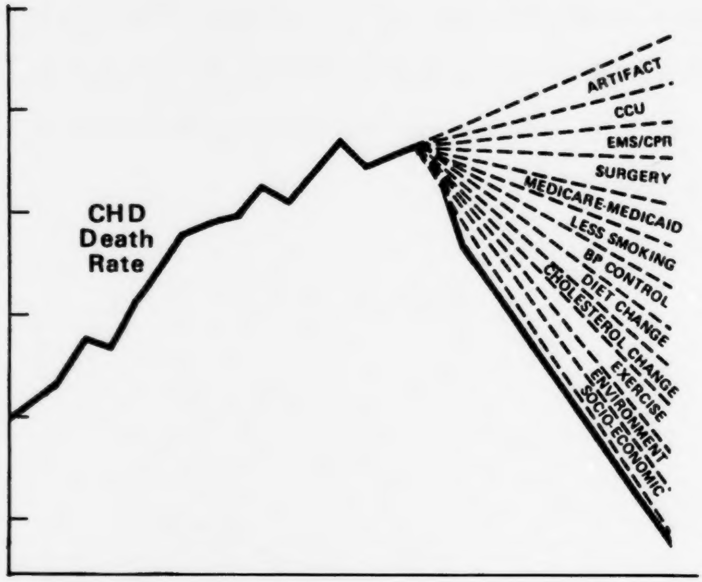


Figure 5. Can We Identify Factors Causing the Coronary Mortality Decline and Measure Their Contribution?

The conference concluded that we did not have enough information to decide which of these factors were contributing to the decline and to what extent each one might be contributing. More information was needed.

Figure 6 reflects some of the epidemiologic evidence relating personal risk factors to the incidence of heart disease. It summarizes the experience of the Framingham Heart Study, which we at the National Heart, Lung, and Blood Institute have been carrying on for over 30 years. This study has related characteristics of people measured early in their lives to their subsequent experience in getting heart disease. You see that for both men and women, heart disease incidence increases markedly with age. When we characterize the population in terms of risk factors (systolic blood pressure, cholesterol levels, cigarette smoking, and glucose intolerance or early diabetes in this case), we see a stratification of the population with more than a 25-fold level of risk between the highest levels and the lowest levels, women and men alike.

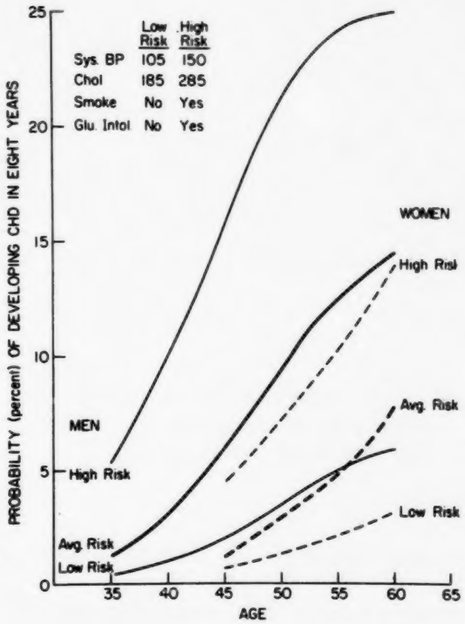


Figure 6. Probability of Developing Coronary Heart Disease in 8 Years by Age, Sex, and Risk Category

What we have discussed are personal risk factors. We do not usually consider them as environmental factors, except perhaps in terms of the personal environment such as cigarette smoking or diet. They have been the factors most heavily concentrated upon by cardiologists and clinicians in trying to abate the heart disease epidemic and in giving advice to individuals about how they might prevent heart attacks. Yet, these personal risk factors can hardly explain what has been going on in different parts of this country.

What Figure 7 shows is the heart disease death rate for each of the 3,000 counties in the United States. The light-colored areas are the lowest percentiles; the darkest ones are the highest percentiles; and the shades of gray are the groups in between. You see that there are obvious geographic patterns of heart disease mortality in the United States which are not due to chance and, so far as we know, are not due to the personal risk factors such as smoking habits, cholesterol levels, or blood pressure. It is very likely that a natural experiment is occurring here which is intimately associated with environmental factors influencing the rates of heart disease. We see that along the southeastern part of the United States, particularly near the coast, heart disease death rates are higher, while in the central part of the country and in the Mountain States, heart disease seems to be at the lowest point. This mapping is based upon 1970 data.

The heart disease mortality rate for 1977 at the state level is reflected in Figure 8. I think you discern a subtle geographic shift in deaths occurring from heart disease in the United States. The Mountain States in the northwestern part of the country still enjoy the lowest rate of

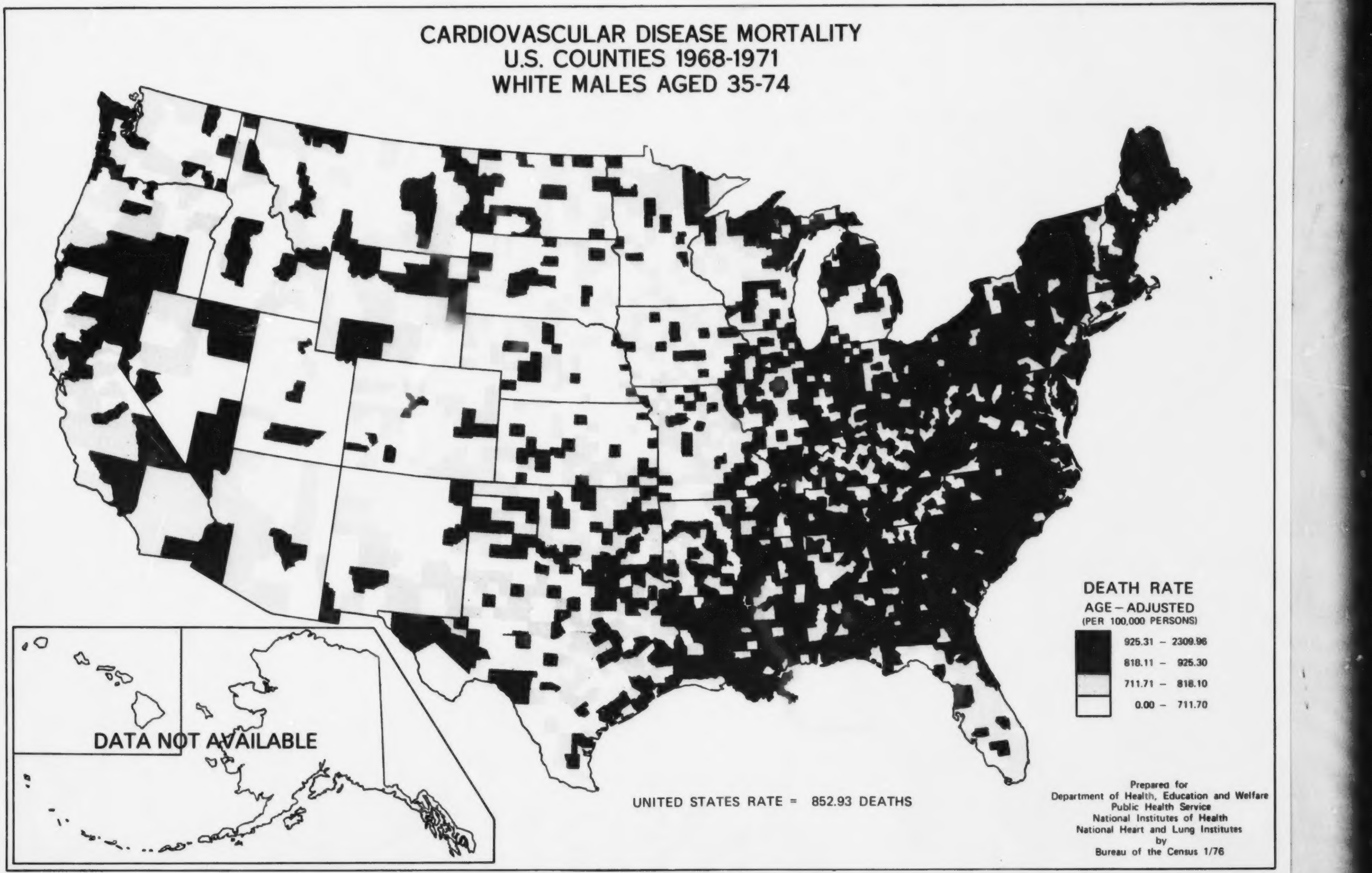

CARDIOVASCULAR DISEASE MORTALITY
U.S. COUNTIES 1968-1971
WHITE MALES AGED 35-74
DEATH RATE
AGE – ADJUSTED
(PER 100,000 PERSONS)
925.31 – 2309.96
818.11 – 925.30
711.71 – 818.10
0.00 – 711.70
DATA NOT AVAILABLE
UNITED STATES RATE = 852.93 DEATHS
Prepared for
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
National Heart and Lung Institutes
by
Bureau of the Census 1/76

Figure 7. Cardiovascular Disease Mortality: U.S. Counties, 1968-71; White Males, Aged 35-74

heart disease. However, you see that the southeastern portion of the country, which still has high heart disease rates, is no longer the very highest, and some of the highest mortality states are now the inland states of West Virginia and Kentucky. This shift away from the coast towards Appalachia, an area which we think has heavy rates of environmental pollution, provides a clue that something might be going on, and perhaps even points to specific environmental factors.

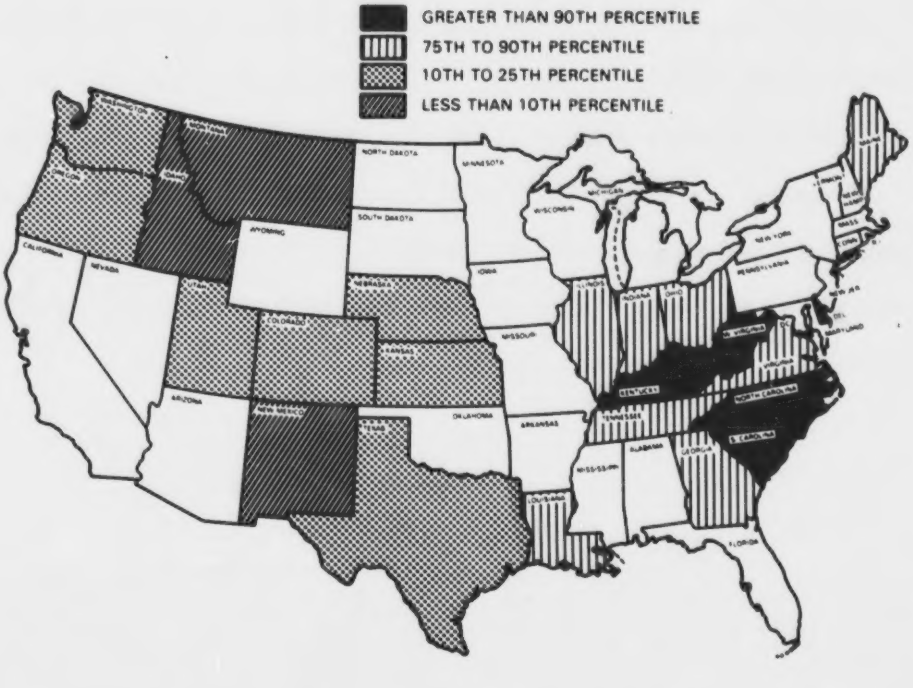

■ GREATER THAN 90TH PERCENTILE
▥ 75TH TO 90TH PERCENTILE
▩ 10TH TO 25TH PERCENTILE
▨ LESS THAN 10TH PERCENTILE
WASHINGTON
MONTANA
NORTH DAKOTA
MINNESOTA
OREGON
IDAHO
SOUTH DAKOTA
WISCONSIN
MICHIGAN
WYOMING
CALIFORNIA
NEVADA
UTAH
NEBRASKA
IOWA
ILLINOIS
INDIANA
OHIO
PENNSYLVANIA
NEW YORK
VERMONT
MASS.
CONN.
NEW JER.
DEL.
MARYLAND
D.C.
COLORADO
KANSAS
MISSOURI
W. VIRGINIA
VIRGINIA
KENTUCKY
NORTH CAROLINA
TENNESSEE
ARIZONA
NEW MEXICO
TEXAS
OKLAHOMA
ARKANSAS
MISSISSIPPI
ALABAMA
GEORGIA
S. CAROLINA
LOUISIANA
FLORIDA

Figure 8. Coronary Heart Disease (410-414) Mortality: White Males, Aged 35-75; Age-Adjusted Rates Per 100,000 (1977)

One of the things we looked at in our program was the obvious relationship between the geographic situation of a country and its heart disease risk. Figure 9 illustrates one aspect of geographic variation--

reported that those people who live at high altitudes have less heart disease than people who live at low altitudes. However, the reports represented only a few isolated places. We decided to look at altitude for all 3,000 counties in the United States. The lower portion of the figure shows the distribution by altitude of the 3,000 counties. As you would suspect, most of the counties lie below 2,000 feet altitude, but some of them, especially in the Mountain States, go up to a mean altitude of 8,000 feet. When we relate the mortality rate to altitude using the counties as the units of observation, we find in the top line a marked inverse relationship between coronary heart disease mortality in men and altitude. A similar trend, though not as visually striking, exists for heart disease in women and for cerebral vascular accidents or strokes in both men and women. It is possible that this marked trend is due to some self-selection of who chooses to live at the high altitude. We think, though, that it might also be attributable to some specific environmental factors, and this hypothesis warrants further investigation.

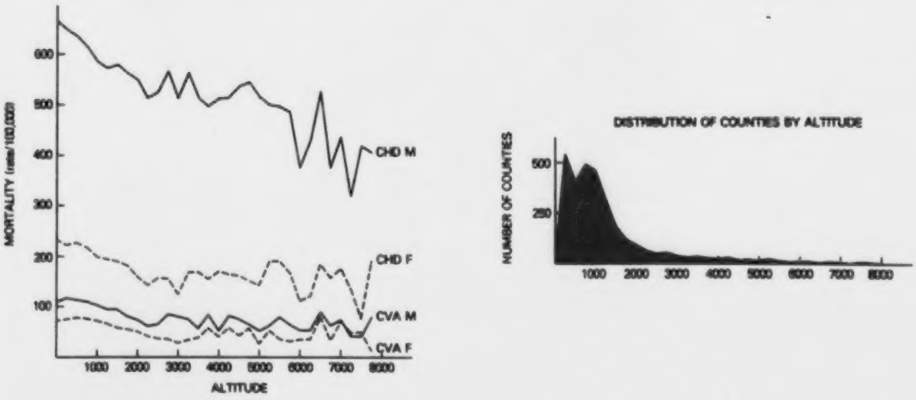


Figure 9. Mortality Versus Altitude by Cause and Sex (Weighted)

Another feature which differs from place to place in the United States is the quality of the water supply. I cannot summarize all of the literature--it is a very intriguing picture--but I would like to present a few details for one particular variable which is of great public health concern. That is the influence of artificial fluoridation upon rates of heart disease around the United States. Our study consisted of classifying all of the cities of the United States with populations over 25,000 into fluoridated and nonfluoridated cities on the basis of whether or not they treated their water supply. We then tracked the mortality rates from 1950 through 1960 to 1970. I hope soon to have the data for 1980.

Figure 10 is rather complicated and requires a bit of explanation. On the far right we see a line with three points over the label "not fluoridated." That line is the experience of 187 communities that have not fluoridated during this period. The topmost point on that line is the adjusted mortality rate in 1950. We see that it is about 1.18. By 1960 it had dropped to about 1.08, and by 1970 it had dropped to about 0.98, indicating what has been going on in the country, a decline in heart disease mortality.

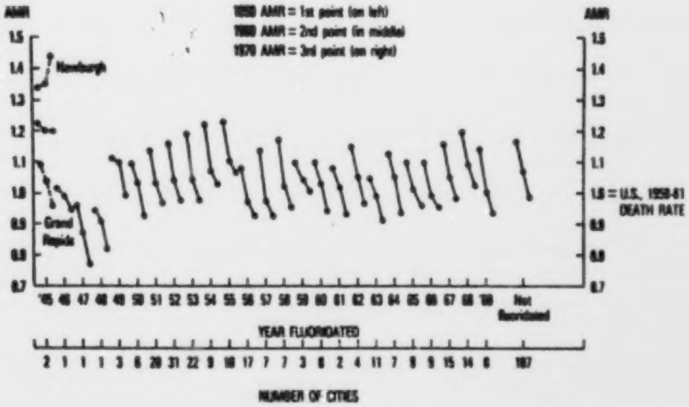


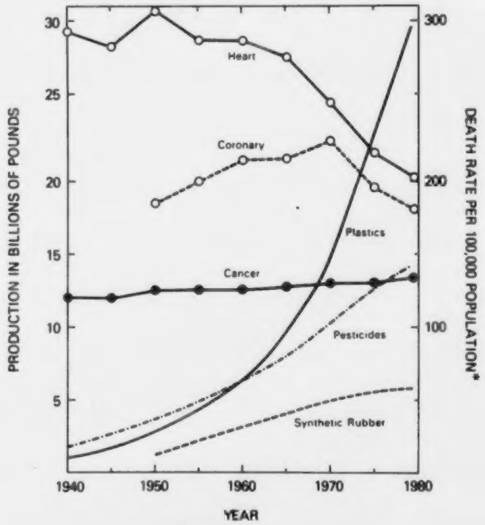
Figure 10. Average Mortality Ratio (AMR) in 1950, 1960, and 1970 Periods for Cities that Fluoridated by Year of Fluoridation and for Cities Not Fluoridating: U.S., Selected Study Cities

Each of the other lines is plotted in a similar fashion. The lines represent clusters of communities that fluoridated in a specific year. For example, the next to the last line on the right over the number 69 represents the eight communities that fluoridated in 1969. Actually for most of the period under observation, they were essentially not flouridated. They fluoridated only in the last year for which we had data, but they showed a similar decline.

Working our way backwards, we find that for different years different communities fluoridated, and they had different starting levels and different ending levels in their mortality rates for heart disease. Yet in every instance, there was a markedly regular decline over this 20-year period.

Looking at the very far left of the figure, only two communities had fluoridated in 1945, Grand Rapids, Michigan, and Newburg, New York. Our story began when we first looked at these data and found that Newburg, contrary to virtually every other city in the United States, had shown a marked increase in heart disease rates during the 20-year period. As you see, Grand Rapids showed a tremendous decline, and virtually every other city that had fluoridated showed a similar decline. At first we thought we had a scandal of some sort on our hands when we looked at the Newburg data, but when we looked at all the other cities in the United States, we were able to conclude that artificial fluoridation had absolutely no effect on the heart disease mortality rate during all the years of its use. Moreover, it is still an effective agent in reducing dental cavities.

Figure 11 illustrates another ecological approach to heart disease mortality and environmental factors. There are two different things going on here. The scale on the right gives the death rate per 100,000 population. Note that heart disease, that is total cardiovascular mortality, was essentially horizontal up to 1950 and then declined from 1950 down to 1980. The dashed line below shows the trend in coronary heart disease rates, the data being first available about 1950. It reflects the same trend that I showed you earlier. The heavy line with the circles in the middle of the figure is the cancer mortality rate during this period. This has actually gone up very slightly. The scale on the left margin shows you the production in billions of pounds of three major chemical products: plastics, pesticides, and synthetic rubber. As you would expect, the use of all three of these substances has been increasing markedly during the last 40 years.



*Age adjusted to 1940 population

ADAPTED FROM: DAVIS, D.L. AND RALL, D.T. 1981. ESTIMATING RISKS AS A BASIS FOR PREVENTION. IN *STRATEGIES FOR PUBLIC HEALTH*, L.K. YNG AND D.L. DAVIS, EDS.

NEW YORK: VAN NOSTRAND, REINHOLD. REPRINTED WITH THE PERMISSION OF D.L. DAVIS.

Figure 11. Heart Disease, Coronary Heart Disease, and Cancer Mortality and Production of Chemicals: U.S., 1940-80

It might have been attractive to relate the gross production of these chemicals (and an assumed relationship between production and environmental pollution) to an increasing mortality rate that had existed. I suppose some people are trying to make a case for this in the cancer field. I think it would be very difficult to relate these kinds of ecological patterns to the decline in heart disease. We have to resort to more specific types of epidemiologic studies to do the kind of research we need for specific exposures in the field of heart disease.

I will not have time to summarize even briefly some of the main features of environmental factors and their influence on heart disease. However, Table 1 cites seven factors which have been found by various investigators related to heart disease. In my mind it is rather interesting that with all the thousands of substances that we are exposed to and the high mortality and morbidity rate from heart disease, only seven substances have been implicated with any degree of hard evidence with regard to heart disease. However, they do reflect a wide variety of exposures--air pollution, particularly carbon monoxide, and the drinking water story we hinted at briefly, for example. Certain heavy metals, particularly cadmium, may have an important effect on the kidney and resulting hypertension. Certain halogenated hydrocarbons are believed to be specific irritants to the conduction system of the heart. They are related to substances that are used in general anesthesia and they might have specific involvement with the nervous system causing arrhythmias associated with heart disease.

Table 1. Environment and Heart Disease

Factor	Type of Study	Effect
• Air Pollution	Ecologic	Non-Specific
• Hardness of Drinking Water	Ecologic	CHD? Sudden Death?
• Cadmium	Animal	Hypertension
• Halogenated Hydrocarbons	Animal	Arrhythmias
• Aliphatic Nitrates	Explosives Manufacturing	Vasospasm
• Carbon Disulfide	Viscose Rayon Industry	CHD
• Carbon Monoxide	Experimental	CHD

Other examples include nitrates such as nitroglycerin, a cardiovascular agent used in the treatment of angina pectoris, which may also cause adverse effects when people are exposed to high doses over a prolonged period of time. Carbon disulfide, a specific solvent used in industry, is believed to be a rather broad metabolic poison and may have specific effects on the lipid system and the likelihood of heart attack. Carbon monoxide has been implicated in the ambient environment and is believed to be one of the more important risk factors with regard to the personal environment due to smoking habits. I think the issues involved with measuring exposure to these substances and metabolism of these substances are what is going to involve this working group during these next 2 or 3 days.

My last illustration (Table 2) can be used to highlight some of the problems we face in studying environmental factors related to heart disease. I have listed here half a dozen task forces and committees that I or members of my staff are currently engaged in vis-a-vis environmental factors in heart disease. They range from this current Task Force to groups dealing with drinking water and geochemistry, bilateral agreements with the Soviet Union, and a wide variety of other factors including things like noise pollution. I get a feeling of deja vu every time I go to one of these meetings. It seems that many of the same people are there dealing with the same problems under the aegis of different agencies. We face very common problems no matter how we try to approach the task at hand. Bob Gordon alluded to many of these problems, and I think one or two of them are worth repeating.

Table 2. Environment and Heart Disease--Interagency Working Groups

Group	Sponsor
• Task Force on Environmental Cancer and Heart and Lung Diseases	EPA
• Safe Drinking Water Committee	NRC
• Panel on Geochemistry of Water in Relation to Cardiovascular Disease	NAS
• Task Force on Environment and the Cardiovascular System	IOM
• US-USSR Cooperative Program in Environmental Health	NIEHS
• Interagency Advisory Group on Noise Effects Research	EPA

The most important one is accessibility of existing data for epidemiological studies of health. I would like to give you one example of an opportunity we had that currently is at an impasse and which illustrates the kind of problem we are facing. As you know, we just finished the largest census in the United States, the 1980 census, in which we enumerated over 225 million people. Approximately 20 percent of the population filled out what is called the long census form, which included a great deal of information about socioeconomic factors, ethnic factors, and, one of the most important to us, occupational factors. We were bold enough to think that we could use these census data source to link to the newly created National Death Index (which you will hear more about tomorrow). The concept was to do a large-scale epidemiological study by matching death records of the National Death Index with census data to produce mortality rates by specific industry, socioeconomic factors, and other issues.

We were well aware of the confidentiality and privacy restrictions. None of the personally identifiable data would be made available, and any studies were going to be done by the Census people or the National Center for Health Statistics people. The summary rates would be reported as they report the current vital statistics data. All agencies seemed very agreeable to this study. We had been working with them for nearly 3 years to get it going. Nevertheless, when we sat down with them this summer to try and finalize our approach to the actual work, everything changed. The main thing was the Census Bureau, which is under attack in the courts about the confidentiality of the files and the adequacy of the reporting, and right now is dealing with 32 lawsuits. They are not disposed to make the data available in any form no matter what safeguards are imposed, even under their own aegis.

The people in the Census Bureau think it is a worthwhile study. They are willing to use the National Center for Health Statistics data. The National Center for Health Statistics thinks it is a worthwhile study. They are willing to use the census data. However, the confidentiality restrictions on both of them prevent them from combining the two data files.

I say this for Congressman Martin's benefit. It may take an act of Congress to get this kind of problem resolved. It is really a fundamental issue, and I think that everybody concerned realizes that the safeguards for confidentiality can be implemented. Studies can be done by the National Center for Health Statistics or the Census Bureau and reported in a safe statistical way. But the legislative mandate under which each Agency works prevents them from bringing their files together for this purpose.

I will not belabor the point--Bob Gordon, I think, spoke very eloquently of the kinds of problems we are having in trying to get the job done. I think there is a willingness and eagerness to get on with the job and try to do these kinds of studies, and I think with the work of this Task Force and with the support of the people who provide the funds, we will be able to make tremendous strides in this area during the next 10 years.

ENVIRONMENTAL FACTORS AND CANCER INCIDENCE

John Higginson, M.D.
International Agency for Research on Cancer

I very much appreciate the dubious honor of being considered capable of covering the problem of environmental cancer in 15 minutes.

When I checked on the intent of Public Law 95-95, I was struck by one thing in Section 402, namely, that Congress had made a distinction between general environmental pollution and other factors that are related to the environment. Accordingly, the mandate of the Task Force is to consider the environment as a whole, and not only in the limiting context of toxic chemicals. Congress also emphasized the importance of prevention.

My background as a pathologist with an interest in cardiovascular diseases conditioned me early to the importance of lifestyle in disease etiology. In contrast to the success that cardiologists have had over the last 30 years in controlling some kinds of heart disease, it is embarrassing to note that no comparable success has yet been apparent in the case of cancer, although lifestyle factors, including cigarette smoking, have been studied for 30 years. However, in the view of the success illustrated by Dr. Feinleib it is interesting to note how little credit researchers get even when they are successful. Success is not regarded as news. Thus, even if oncologists eventually manage to prevent a great number of cancers through elimination of cigarette smoking, it is unlikely that the success of this action will be recognized.

The present program contains much on toxicology, a subject about which I know little. So, I have decided to address myself largely to other environmental factors which may be pertinent to later activities of the Task Force. Due to the limitation of time, it will be impossible to justify some of my more sweeping statements.

In recent years, we have increasingly recognized the complexity of the cancer problem, and the fact that it cannot be discussed only in terms of initiation. While direct or indirect environmental initiators are important, genotoxic carcinogens are insufficient to explain much of the cancer problem. There is no doubt that events within the cell before and after initiation are complex and highly relevant to carcinogenesis, and this confirms the view of earlier epidemiologists and experimentalists, who for years, against much opposition, emphasized the importance of modulating environmental factors. Today, however, epidemiologists and experimentalists are beginning to talk the same language. Further, all are in agreement that cancer is multifactorial. This was stressed as early as 1950, and the well-known synergism between alcohol and tobacco, asbestos and tobacco, etc., was demonstrated many years ago. Furthermore, we now know that there are numerous factors in the environment that inhibit carcinogenesis.

However, while it is inaccurate to consider cancer causation in terms of single causes, it may be practical to prevent cancer through control of a single factor. Thus, Dr. Selikoff has emphasized that asbestos as a public health problem would disappear to a great extent if workers exposed to the fiber would cease smoking, and no man knows the problem better than he.

Further, the recognition of the complexity of carcinogenesis, and the fact that initiation alone may be insufficient, again indicates the great difficulties of extrapolation from animal systems, a point to which the Task

Force must address itself. The literature is full of comments on the inadequacies of the epidemiologic method, with the implied corollary that extrapolation is more precise. The fact that, in the present limited state of our knowledge, we use animal models to identify potential future dangers does not mean that these models are any more exact or better than the epidemiological or human data. In fact, the evidence is to the contrary. It simply means that in environmental carcinogenesis we must make the best of unsatisfactory and imprecise tools. The obvious conclusion is that it is necessary for the Task Force to come up with parameters more easily measured and more relevant, and also to identify better models.

In discussing the causes of human cancer, it is unnecessary to review further point-source exposures and cultural habits, for example, cigarettes, occupation, etc. However, we still do not know the cause of about 70 percent of cancers in women and 40 percent of cancers in males. In relation to their importance, the causes of female cancers have been little studied, even if we know them to be environmental. Cancers of unknown origin include tumors of the gastrointestinal tract and cancers of the breast, uterus, and ovaries. As a matter of interest, the incidence of stomach cancer has decreased considerably, for reasons that we do not know.

Two major theories are held regarding this large group of cancers. First, that they are due to general pollution and that constant exposure to multiple initiators in small doses leads to numerous transformed cells in the body. Thus, these factors represent the basic cause. On the other hand, extensive studies of total pollution, e.g., air pollution, indicate no significant differences between highly polluted cities and nonpolluted cities.

People have repeatedly tried to describe a role of ambient pollution in cancer, and such studies have been duplicated both in the United States and in the United Kingdom over many years. However, geographical distribution and time trends are not consistent with this hypothesis. The widely demonstrated increase in lung cancer is almost entirely due to cigarette smoking. Similarly, the limitations of time trends are not appreciated. The major increase in breast cancer which took place in 1975 largely resulted from increased consciousness of the disease following an operation on a President's wife. This does not mean that environmental pollution should not be controlled, but it means that apart from cigarette smoking and certain obvious point-source exposures, such action will have relatively little effect on the cancer problem. There are other very good reasons for controlling air pollution.

I do not wish to discuss time trends further, but all that we can say is that over the last 10 years, whilst people have been trying to establish new baselines for examining incidence, changes apart from lung cancer have been minimal. Further, such changes cannot be ascribed to increases in the use of organic chemicals, pesticides, etc. In fact, there is no correlation between manufacture and exposure. Thus, in London the amount of air pollution has decreased, as have occupational exposures in the workplace in most industrial countries. On the other hand, as Dr. Feinleib has pointed out, there have been very marked changes in the United States and Australian diets, i.e., a 50 percent increase in consumption of unsaturated fats and nearly a 40 percent reduction in saturated fats. We know that fatty acids may promote cancer in certain classical animal experiments, and we cannot, therefore, ignore such dietary changes, as well as behavioral changes, when examining temporal change in cancers of the colon and rectum and other sites.

The point that I wish to emphasize, therefore, is that while we have been able to observe marked changes in the incidence of cardiovascular disease, possibly related to diet, we have no idea as yet what such dietary changes are doing in cancer. For example, if, as several studies suggest, dairy products protect against gastric cancer and there is a reduction in the intake of such products, it is possible that an increase in stomach cancer may occur. This would indicate that we must be cautious in making definitive suggestions to the public as to lifestyle changes without taking more complex factors into consideration. In making recommendations with regard to one disease, we must consider effects on others. Besides being remiss in studying dietary factors, we oncologists have been equally remiss in our evaluation of behavioral patterns.

These remarks all indicate that very careful considerations must be given to what is termed lifestyle factors. In the United Kingdom, there are very clear relationships between different social classes and their lifestyles and corresponding cancer frequencies. In that country, it is believed that nearly 90 percent of the variations in cancer risk between occupations are due to lifestyle and only approximately 12 percent due to potential exposures. Moreoever, we find that these lifestyle changes affect not only the worker, but also his wife. Thus, for example, the overall mortality among fishermen's wives in the United Kingdom, like that in their husbands, is almost 77 percent higher than normal, in contrast with the good health of civil servants and their wives. The members of the petrochemical industries and their wives have an average mortality experience. Cancer among the wives of transport workers is high, and this is generally attributed to the stress associated with the fact that their husbands are away from home, leading them to smoke and drink more. In other words, in discussing cancer, we are discussing a total social phenomenon. Fifty-two percent of Americans now work in offices, and 3 to 4 percent work in agriculture. Furthermore, we have a new group of skilled blue-collar workers who, through modern technology, are more likely to be subject to the problems of "misnutrition" than "undernutrition." We must not forget that too much smoking and excessive alcohol drinking are related to a deprived lifestyle associated with poverty or frustration, and this is a form of social pollution. However, many people consider this a dangerous statement. Nevertheless, as scientists, we must remember that we are elitist and that we have a duty to examine the life and dangers for those less privileged than ourselves in a total sense.

While emphasizing the importance of lifestyle, we are still unsure of mechanisms in many cases. However, these observations offer a great intellectual challenge to scientists. Today, for the first time, we are attempting to explore lifestyle and cancer more objectively through metabolic or biochemical epidemiology, e.g., the biochemical impact of first pregnancy, liver enzyme activity, detoxification and activation of carcinogens, promotion and inhibition, and so on. These are new fields, and it will probably take us more than 10 years to come up with overall answers meaningful for prevention. In the early stages, such work may be pedestrian and difficult. Accordingly, I feel strongly that short-term granting mechanisms unfortunately are not likely to provide a suitable method for supporting this type of research, which will require systematic and long-term studies. I hope that the Task Force will consider this problem. It is doubtful if we could today get the resources to carry out the Framingham Study, and yet this has been a source of a tremendous amount of useful information, and it is regrettable that we have no comparable study in the cancer field. It is essential to think of the long-term program, to forget our generation, and remember that it is our duty to benefit our children.

In conclusion, the thought with which I would like to leave you is that cancer is a problem of the total community and not of limited social groups. We should set our priorities towards getting the maximum bang for the buck, and take public health steps that are going to have the greatest impact, before we spend considerable amounts of money on the fine tuning, which can come later. We must remove from the public mind the belief that every initiator or carcinogen, no matter how minimal the exposure, must be controlled, or that cancer is a simple process of controlling such initiators. It represents a much more complex intellectual challenge to the scientist of the future.

RESEARCH AND REGULATION IN ENVIRONMENTAL HEALTH

Richard Dowd, Ph.D.
U.S. Environmental Protection Agency

Although I feel very humble after the last several talks, I think that the conference has already gotten off to a fertile start, and I think as representing an Agency, I have a lot less to say in terms of scientific content of your discussion.

I would like to put my remarks in the context of some of the issues that need to take place in a regulatory Agency, so I will try to move fairly quickly so that we can hear Congressman Martin, who I think will probably have more important things to say.

I am delighted to be here this evening addressing the Workshop on Exposure, Metabolism, and Mechanisms of Toxicity because the subject is of particular interest in understanding the effects of environmental pollutants on human disease.

As you know, the Task Force on Environmental Cancer and Heart and Lung disease was established by the Clean Air Act Amendments of 1977 to focus efforts by the Environmental Protection Agency and the various branches of the Department of Health and Human Services on the development of coordinated, comprehensive Federal research programs and strategies for reducing the risks of environmentally related cancer and heart and lung disease.

This focus on the environment, with the Administrator of EPA as the Chairperson of the Task Force, has been instrumental in defining the contribution of environmental pollutants to human disease, and developing an interagency capability to address this problem.

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Within this framework, the identification of available Federal resources and the initiation of information exchange of Task Force members has already been a valuable accomplishment.

EPA's health effects research is one of the Agency's most critical areas of research. Most of the Agency's regulations and standards are based on the effects of environmental pollutants on human health. I would like to devote my remarks to the role of environmental health research in the regulatory process.

For the most part, the health effects research needed to support each of these standards and regulations focuses on governmental research which involves developing and validating test methods and experimental protocols.

Currently the Environmental Protection Agency's research program follows four basic lines of inquiry. First, what is the range of human diseases that could result from exposure to environmental pollutants? Second, what test systems are necessary to detect pollutant-induced disease processes? Third, what critical life processes impact on quantitative extrapolation in species? Fourth, how does man's sensitivity to particular types of toxicity correlate to that of test animals or test systems?

These four lines of inquiry lead to one of the major purposes of the Agency's health effects research in the regulatory process, and that purpose is the determination of the levels of risk that are associated with exposure to different concentrations of a pollutant.

This requires a knowledge of the dose-response curve and of the level and extent of individual and population exposures. The outputs of a risk assessment can be manyfold, but two have been shown to be generally useful: (1) an estimate of the increased probability of disease or death of an individual as a function of increased exposure; and (2) a body count of the morbidity or mortality within a population for any given exposure.

Ideally what could be provided by health data is a dose-response curve at levels of concern. For the Environmental Protection Agency, dose-response curves are needed at low levels of exposure (indeed, by toxicologic standards, very low levels) and for chronic as well as acute exposures. This situation, while understandable in theory, is much more complicated in practice, as we have heard over the last few minutes.

Derivation of clear, precise dose-response curves at low levels requires, first, a clear definition of the health or disease endpoint itself. Second, the ability to extrapolate from relatively high doses to the much lower dose and often to extrapolate from test animal data to man is typical of environmental exposures. Third, we need the generation of good, sufficient data.

Because of difficulties in producing dose-response data for, in part, determining health endpoints, solving extrapolation problems, and mitigating the lack of good data, exact scientific assessments of health risks imposed by exposure are generally very difficult.

In order to look at the problem from a different angle, we now think that short-term tests will be able to produce data that are quantitatively sometimes more useful to a large part of the regulatory process.

In the process of developing and validating short-term tests, mechanisms of toxicity will become much better defined, thereby greatly improving the precision of the dose response curves, we hope, and hence the risk assessments. Similarly, short-term tests may be developed that can be used in large-scale surveys of human populations such as rapid and accurate measures of enzyme activity or the morphology and motility of spermatozoa, thereby again making epidemiology a more powerful and useful source of data.

It is important to understand that the standard-setting process is not wholly scientific, but is profoundly political. The question of where to set a limit cannot be considered separately from social and economic factors such as cost and benefits.

However, the role of science is a very important factor. The scientific data provide a factual, intellectual foundation for our regulations and provide a framework for understanding what the standards and regulations should reflect to the degree that such a consensus does exist in the scientific community. When there is no agreement in the scientific community on the interpretation of scientific data, and we all know of many cases where that is true, then the regulatory Agencies must decide what to do in the face of this scientific uncertainty. In order to do this in a responsible and acceptable way, Agency decisions must reflect the judgments, take into account issues of public concern, and be more open according to the precepts of fairness and the mandates embodied in the law.

In closing, I would like to reiterate that your job over the next few days is an extremely important one. The identification of research needs in the area of exposure and metabolic mechanisms and the proposal of research strategies to meet these needs will be an important contribution to guiding the research efforts now focusing on the contribution of environmental pollutants to environmental cancer and heart and lung disease.

CONGRESSIONAL PERSPECTIVES ON ENVIRONMENTAL RESEARCH AND REGULATION

Hon. James G. Martin, Ph.D.
United States House of Representatives

I do consider that it is an honor to be invited to participate in this workshop, to be here along with eminent scientists. They have broadened the adjective and spelled it i-m-m-i-n-e-n-t so that I could participate, and I appreciate that very much.

I do seriously want to commend you and encourage you for the work that you are undertaking here in this series of meetings, both in the larger Task Force and also this Workshop Working Group which is seeking to develop a basis for better direction and better coordination of research in prevention and reduction of environmentally related cancer and heart and lung disease.

From reviewing some of the materials that have been available to me, including past reports of the Task Force, I commend you for the high quality of the efforts that you have exerted in trying to meet the demands of the 95th Congress. I've come here this evening, Dr. Gordon, to say that what we really need is better information about nutrition and low-level radiation risks. So back to work.

You do have to understand that some of my observations will obviously be years behind, hopefully not decades, but years behind ideas that you have already thought through, some of which you have explored and failed to realize, some of which you have rejected. But even this limited progress will reveal the extent to which one member of Congress is beginning to catch on to some of the research needs in your areas--or not catch on, as the case may be.

Yes, it is true that I am a scientist, but I am not an omniscientist. I like to play with words like that. You'll have to forgive me when I get one off from time to time.

Too often it has been true in the past that Congress has looked to you and said to you, "Science, we want pat answers. We want yes/no answers. We want pass/fail grades. We don't want anymore of the proverbial two-handed scientists telling us 'on the other hand'," as several of you did here this evening.

One of the challenges lying ahead is to educate the Congress in some way and to help us to translate some of the complexities of what you're dealing with. Too often the pat answer, if it's wrong, distracts you from what you really need to be about, especially when you get into those multifactorial modulators, Dr. Higginson. That will bring them to their knees. We must find a way to express from the scientific community, and from the research institutions of government and academic institutions as well, how we feel when Congress asks you to come up with information that you regard as foolish or makes foolish requests. There should be some polite, courteous way to say, "Please, ma'am or sir, it won't mean anything if we tell you the answer to your question when there are a lot more important things that we need to be addressing such as the recommendations that will come out of your reports rather than the recommendations that come out of these bills that you cite. We just throw those in from time to time to get your attention and see if there is really something there."

Speak up about these reservations. Find a way to express your own feelings. If you prefer to speak to someone in private, then speak to some of us about it privately. Help us, and I'm speaking of my colleagues, to see the very great need that we have in this country for a greater emphasis on basic research and fundamental investigations, to improve our understanding of what's going on in the subject that you're addressing.

Certainly testing has its place, testing substances to see which are factors and which are not. Testing is valuable for identifying hazards, but it's not a substitute for fundamental inquiries into the causes and the relationships of the mechanisms, etc., that is, into the nature of things that are in your professional specialty.

It has been noted that this year the Clean Air Act will come up for extension and reauthorization in the Congress. It will be reauthorized; it will be extended. There are also likely to be some changes.

I would say that we need to assist the Congress in focusing on the scientific basis for what health standards should be. Early on, as the Congress first looked into this area and other regulatory authorizations, Congress too often found itself in a position of not knowing what to do, and therefore created a mechanism whereby an Administrator was told, "Go ye forth into ye streets and do ye thing." In other cases, Congress, rather than being too general, got too specific. Too often it was just a numbers game: pick a number! Let's get some number, some standard, in order to get things moving.

Today, you've got to face the fact that there is something of a counter-regulatory mood abroad in the land; if you understand politics, that means that there is a counter-regulatory mood abroad in the Congress. What we must do is find ways to hold the line on those standards that are based on evidence, because it's not going to be easy to hold the line on those that were selected simply on the basis of trying to force technology for no purpose other than to force technology. You may agree or disagree with that approach, but I think you've got to anticipate it. The same thing will apply to the Clean Water Act when its turn comes. The 92nd Congress could be forgiven for assuming that water could be made absolutely pure or that it even should be for biological sustenance, but the 97th Congress must learn a better scientific perspective, in my opinion.

Another area that's going to come up for examination in this forthcoming Congress is one that some of us have discussed, debated, and argued over for the last 3 years, and it is a subject that, before March of 1977, we could not debate very well--the Delaney clause. Prior to 1977, anybody who proposed any modification of the Delaney clause of the Food, Drug, and Cosmetic Act was accused of being in favor of a little bit of cancer. No politician can go back home and face the folks when the opposition is making an accusation of that sort.

Somehow--it is one of the marvels of sociopolitical developments in this country--that all changed when the FDA was required to ban the last of the artificial sweeteners, saccharin. At that point, members of Congress who would not have even considered whether that prior legislation, enacted in 1958, needed changing were deluged with mail demanding that they come up with ways to stop this ban--bomb the ban on saccharin. There was more mail on that subject than on such more profound issues as the bombing of Cambodia, the mining of Haiphong Harbor, and even, in some instances, the impeachment of Richard Nixon. We don't say that saccharin was a more profound issue than those, but it was one that directed the attention of a lot of people to an issue that finally, this year, is going to be examined.

There was a time when we could be assured that our food supply was pure because we had gifted analytical chemists with techniques that could find as little as one part per million, and we were assured by food scientists that there was nothing there to worry about. Today, some of you who are in that profession, not out of mischief but out of just trying to improve the quality of your work, are detecting parts per trillion, a millionth of a part per million. No one who has studied Avogadro's number can believe that that's the end. That sensitivity threshhold is going to continue to move. Likewise, testing techniques, using more and more sensitive techniques for testing, have succeeded in indicting and convicting a large array of substances. My hope is that Congress, with your help, will develop a policy of a risk perspective whereby we will be evaluating relative risk factors, perhaps along the line that Dr. Dowd and his colleagues and other Agencies have been exploring.

It is difficult to have a precise estimate of a relative risk in relation to another imprecise risk, but it seems to me that that's far better than a standard which says in effect that no benefit, no matter how great, justifies a risk, no matter how small. There has to be some evolution away from that absolute zero risk standard, in my opinion--a debatable subject, one which I invite you to debate, no matter which side you're on.

It seems to me that our available resources--political resources, resources of popular support for what you are doing and for what we are doing, funding resources--can better be utilized if we have some idea of which risks are believed to be greater, and which are believed to be relatively minor, even if our beliefs are imprecise by several orders of magnitude.

Obviously we can't ban everything known to be as carcinogenic as saccharin, nor, it seems to me, can we really paper over the universe with warning labels for everything that will be found to fit that category.

You know the story of crying wolf too often. Already people ignore the warning labels. There have to be three of them in triplicate in every grocery store, and they are more terrifying than the warning label on the package of high-tar, high-nicotine cigarettes. You didn't think I would use that word here, being the North Carolina representative, did you?

We've got to develop a better understanding of where the real wolves are and start with the worst ones. In a sense that brings you back to the point that I believe Dr. Gordon had made earlier this evening, that we must develop a greater appreciation for, reliance on, and use of the statistical techniques of epidemiology.

Epidemiological analysis won't detect every factor, but it will direct your attention to the worst ones. Epidemiological analysis won't prove the absolute safety of something that doesn't show up on those graphs, but it will give you some idea of a limit below which that substance poses a risk factor, otherwise it would have been detected. So let's not neglect that in trying to seek out everything in the chemical abstract that can be identified as having a risk.

If we do so, we're bound to encounter some instances where we run up against those lifestyle choices that have been referred to this evening by Dr. Higginson, choices ingrained in us and our neighbors and our constituents by habit, by ethnic values, by pleasure, by other psychological leads that we can barely grasp, especially when it's the other person's choice. Still, we can, if we have a good scientific basis for what we are saying, focus our educational programs on those major factors in hopes of changing some minds. It seems to me that we will accomplish far more insofar as public health is concerned if we change some minds in that way than by using the force of government to deprive people of choices involving relatively remote risks.

It seems to me that we need to be able to differentiate on the question of what constitutes--let's call it unacceptable risks, since no one can define an acceptable risk. We need to find ways to differentiate degrees of unacceptable risks in terms of those that are voluntary and those that are involuntary, and we need to examine alternative choices with these considerations in mind.

I have been pleased to note that you are addressing the need for improving the standardization of measurements and testing. This can certainly give you greater confidence in interpreting for the rest of us the reliability and the meaningfulness of scientific data.

I would suggest to you further that some thought be given to examining whether in some cases the positive pathology results that are obtained only at very large doses merely indicate what it takes to overwhelm what little defense mechanism remains in our test animals. Can't such questions be asked by scientists? Can't such questions be answered?

It seems to me that if we can find answers, we'll have a better basis for developing sound public policy with regard to regulating carcinogens; otherwise I feel reasonably confident, though this may be an overstatement, that ultimately we will succeed in ending up with three categories of chemicals, not the same three categories that OSHA proposed in its regulation on workplace carcinogens, but somewhat similar. They will be (a) those chemicals that have been shown to be carcinogens, (b) those chemicals that eventually will be shown to be carcinogens, and (c) those that are too toxic to be administered in a high dose long enough to produce tumors. I told you it was going to be an overstatement. We need a better basis for the national policy that must evolve as a rational policy for regulating carcinogens. There does need to be, and I'm glad to see that you're addressing this need, increased emphasis on studies of metabolism; otherwise, you can't be sure that what you're testing is the right substance, whether it's a precursor or a successor.

I hope that finally you will help us to understand whether our efforts, and yours, are being rewarded by some of the progress that Dr. Feinleib addressed with regard to cardiovascular disease and that Dr. Higginson referred to in his notes.

As far as cancer statistics are concerned, for example, two interpretations have been presented to committees of Congress with regard to whether one trend line represents progress or an epidemic. It has been pointed out to us that cancer rates have been declining within age groups, with the exception of lung cancer, and that would seem to indicate progress.

But it has also been strongly pointed out that the danger is acute, it is real, it is immediate, it is epidemic because there have been increasing rates of cancer/future risk prospects for people within a given age group, without pointing out that that's just because these people are now more likely to live longer, escaping cardiovascular disease. Within an age cohort there has been a decline with the exception that I mentioned. If I'm wrong about that, you'll point it out to me either here this evening or with anonymous correspondence at your leisure.

I urge you and your colleagues to help us, through your official duties but also individually and through the learned societies of which you are members, to speak out more frequently about questions of public policy relating to science, especially to present opposing sides.

I have seen too many examples of people whose careers have been thwarted within our Government because they didn't adhere to a certain orthodoxy of view, and I don't propose, with the change in administration or congressional influence, to sit idly back and just see a different group of people have their careers blunted and thwarted and intimidated, but rather to help you to present that conflict, that controversy that is within science. Somehow we can help nonscientists to have a better understanding of the limitations of science, about the controversies of science, about the meaning of science, if we are able to express those views.

We ought to hear opposing views such as on how to save the privacy dilemma that a couple of you have spoken about, on the question of the Delaney absolute versus relative risk approach, and on the risk tradeoffs that we have. You can't just advise people that it is unhealthy to go outdoors and it's dangerous to stay indoors. Again, I overstate for effect.

Above all, to go back to my first point, we must persuade Congress of the need for fundamental research. Too often the nonscientist member of Congress, just like the nonscientist member of the public at large, can't remember that relationship. If you think there is a different ideal about political leadership, it's because you think that it's all on the level. It's the public will that determines what the congressional will in most instances is going to be.

Too often the nonscientist in both segments wants to see the immediate practical payout. We'll pay billions of dollars to haul everything off the shelf and run it through all of our instruments. But if somebody comes up with a funny-sounding research title, by darn we're going to root them out and we're not going to waste our hard-earned tax dollars on that kind of work.

So we've got to help more and more members of Congress understand the vital need for the fundamental examinations, the fundamental inquiries that arise because of the extent of reading and training that you and your colleagues and those in other disciplines have been privileged to exercise.

You've got to help us to set science policy. Don't expect the public or the Congress to turn over full jurisdiction to scientists for determining public policy with regard to science questions. We should look to no one else but scientists to interpret for us the meaning of science and the meaning of scientific evidence.

So get back to work.